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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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NOVEL IFNgamma-LIKE POLYPEPTIDES

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NOVEL IFNgamma-LIKE POLYPEPTIDES

FIELD OF THE INVENTION

The present invention relates to nucleic acid sequences identified in human genome as encoding for novel polypeptides, more specifically for novel polypeptides having at least one activity of human Interferon gamma.

BACKGROUND OF THE INVENTION

Interferons (IFNs) are cytokines that play a complex and central role in mammalian immunological response to pathologic events such as infections, immunological disorders, and neoplastic degenerations.

There are two groups of IFNs: type I (IFNalpha and IFNbeta) and type II (IFNgamma, also known as immune interferon). IFNgamma is a cytokine produced by T-lymphocytes and natural killer cells and exists as a homodimer of two noncovalently bound polypeptide subunits, found in different glycosylated forms (Younes HM and Amsden BG, 2002; Boehm U et al., 1997).

IFNgamma is a potent activator of mononuclear phagocytes, capable of affecting immune response by inducing the expression of several molecule, including tumor necrosis factor (TNF), class I / II major histocompatibility complex (MHC) molecules, and the enzymes mediating the respiratory burst which allow macrophages to kill phagocytosed microbes and tumor cells. IFNgamma triggers, by binding its cell surface receptor and activating intracellular signal transduction (JAK-STAT pathway, in particular), not only T and B-lymphocytes differentiation and the cytolytic activity of natural killer (NK) cells, but also the apoptosis or the proliferation of other cell types, such as vascular endothelial cells, also by modulating tryptophan metabolism.

The cellular responses to IFNgamma are particularly complex also because this protein coordinates many different cellular events. Moreover, IFNgamma may have agonistic, as well as antagonistic, properties which can be cell type-specific.

Important therapeutic properties of IFNgamma, alone or in combination with other compounds, have been suggested and/or demonstrated for a broad range of indications including Interstitial Pulmonary Fibrosis (Ziesche R et al., 1999), asthma (WO 01/34180), or septic shock (Docke WD et al., 1997). In cancer immunotherapy, IFNgamma is injected along with irradiated autologous tumor cell, since it acts as an adjuvant and enhances the immune response to the tumor cell challenge. IFNgamma is currently is approved by the Food and Drug Administration (FDA) for limited clinical uses (such as for the reduction of infections associated with chronic granulomatous disease and for delaying progression in patients with malignant osteopetrosis), since this protein also yields significant side effects, such as fever, fatigue, nausea, and neurotoxicity.

These limitations, probably due to the expression of IFNgamma receptors on the surface of almost all types of human cells and the consequent excessive signaling activities (Bach EA et al., 1997), have prompted the development of alternative forms and delivering systems for this cytokine to achieve more acceptable results. Various naturally-occurring or synthetic forms of the human IFNgamma have been described, having longer or shorter N- / C-terminal sequences, or mutated in specific residues for improving specific properties such as heat-stability (WO97/11179) or glycosylation (WO 02/81507).

The literature provides many examples of different approaches for characterizing novel proteins by making use of bioinformatics analysis of transcripts, for example for chemokines (Wells TN and Peitsch MC, 2000). For example, GB patent application No.

0130720.6 discloses a novel polypeptide sequence, called INSP037, matching structural features of IFNgamma.

Since the actual content in DNA sequence in human genome encoding for IFNs (and for any other protein family) is still unknown, the possibility still exists to identify DNA sequence encoding polypeptide having IFNgamma-like structure and activity by applying alternative homology/structural criteria to the totality of Open Reading Frames (ORFs, that is, genomic sequences containing consecutive triplets of nucleotides coding for amino acids, not interrupted by a termination codon and potentially translatable in a polypeptide) present in human genome.

SUMMARY OF THE INVENTION

The invention is based upon the identification of Open Reading Frames (ORFs) in human genome encoding novel IFNgamma-like polypeptides on the basis of the homology with INSP037.

Accordingly, the invention provides identifies polypeptides having the amino acid sequence given by SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40, their mature forms, variants, and fragments, as polypeptides having at least one activity of human IFNgamma. The invention includes also the nucleic acids encoding them, vectors containing such nucleic acids, and cell containing these vectors or nucleic acids, as well as other related reagents such as fusion proteins and ligands.

The invention provides methods for identifying and making these molecules, for preparing pharmaceutical compositions containing them, and for their use in the diagnosis, prevention and treatment of diseases where compounds having at least one activity of human IFNgamma may provide positive effects.

DESCRIPTION OF THE FIGURES

Figure 1: alignment of IFNFH01 ORF (SEQ ID NO: 1) with pIFNFH01 protein sequence (SEQ ID NO: 2). The residues found identical in INSP037 are underlined (71% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH01_5 (forward, SEQ ID NO: 41) and CL_IFNFH01_3 (reverse; SEQ ID NO: 42) in the ORF sequence.

Figure 2: alignment of IFNFH03 ORF (SEQ ID NO: 3) with pIFNFH03 protein sequence (SEQ ID NO: 4). The residues found identical in INSP037 are underlined (73.5% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH03_5 (forward; SEQ ID NO: 43) and CL_IFNFH03_3 (reverse; SEQ ID NO: 44) in the ORF sequence.

Figure 3: alignment of IFNFH04 ORF (SEQ ID NO: 5) with pIFNFH04 protein sequence (SEQ ID NO: 6). The residues found identical in INSP037 are underlined (73.5% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH04_5 (forward; SEQ ID NO: 45) and CL_IFNFH04_3 (reverse; SEQ ID NO: 46) in the ORF sequence.

Figure 4: alignment of IFNFH08 ORF (SEQ ID NO: 7) with pIFNFH08 protein sequence (SEQ ID NO: 8). The residues found identical in INSP037 are underlined (78.5% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH08_5 (forward; SEQ ID NO: 47) and CL_IFNFH08_3 (reverse; SEQ ID NO: 48) in the ORF sequence.

Figure 5: alignment of IFNFH10 ORF (SEQ ID NO: 9) with pIFNFH10 protein sequence (SEQ ID NO: 10). The residues found identical in INSP037 are underlined (69.5% of identity with INSP037). The arrows indicate the

position of the primers CL_IFNFH10_5 (forward; SEQ ID NO: 49) and CL_IFNFH10_3 (reverse; SEQ ID NO: 50) in the ORF sequence.

Figure 6: alignment of IFNFH11 ORF (SEQ ID NO: 11) with pIFNFH11 protein sequence (SEQ ID NO: 12). The residues found identical in INSP037 are underlined (73.5% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH11_5 (forward; SEQ ID NO: 51) and CL_IFNFH11_3 (reverse; SEQ ID NO: 52) in the ORF sequence.

Figure 7: alignment of IFNFH12 ORF (SEQ ID NO: 13) with pIFNFH12 protein sequence (SEQ ID NO: 14). The residues found identical in INSP037 are underlined (73.5% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH12_5 (forward; SEQ ID NO: 53) and CL_IFNFH12_3 (reverse; SEQ ID NO: 54) in the ORF sequence.

Figure 8: alignment of IFNFH13 ORF (SEQ ID NO: 15) with pIFNFH13 protein sequence (SEQ ID NO: 16). The residues found identical in INSP037 are underlined (69.5% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH13_5 (forward; SEQ ID NO: 55) and CL_IFNFH13_3 (reverse; SEQ ID NO: 56) in the ORF sequence.

Figure 9: alignment of IFNFH14 ORF (SEQ ID NO: 17) with pIFNFH14 protein sequence (SEQ ID NO: 18). The residues found identical in INSP037 are underlined (71% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH14_5 (forward; SEQ ID NO: 57) and CL_IFNFH14_3 (reverse; SEQ ID NO: 58) in the ORF sequence.

Figure 10: alignment of IFNFH15 ORF (SEQ ID NO: 19) with pIFNFH15 protein sequence (SEQ ID NO: 20). The residues found identical in INSP037 are underlined (71% of identity with INSP037). The arrows indicate the position

of the primers CL_IFNFH15_5 (forward; SEQ ID NO: 59) and CL_IFNFH15_3 (reverse; SEQ ID NO: 60) in the ORF sequence.

Figure 11: alignment of IFNFH20 ORF (SEQ ID NO: 21) with pIFNFH20 protein sequence (SEQ ID NO: 22). The residues found identical in INSP037 are underlined (67% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH20_5 (forward; SEQ ID NO: 61) and CL_IFNFH20_3 (reverse; SEQ ID NO: 62) in the ORF sequence.

Figure 12: alignment of IFNFH23 ORF (SEQ ID NO: 23) with pIFNFH23 protein sequence (SEQ ID NO: 24). The residues found identical in INSP037 are underlined (72% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH23_5 (forward; SEQ ID NO: 63) and CL_IFNFH23_3 (reverse; SEQ ID NO: 64) in the ORF sequence.

Figure 13: alignment of IFNFH25 ORF (SEQ ID NO: 25) with pIFNFH25 protein sequence (SEQ ID NO: 26). The residues found identical in INSP037 are underlined (70% of identity with INSP037).

Figure 14: alignment of IFNFH27 ORF (SEQ ID NO: 27) with pIFNFH27 protein sequence (SEQ ID NO: 28). The residues found identical in INSP037 are underlined (68% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH27_5 (forward; SEQ ID NO: 65) and CL_IFNFH27_3 (reverse; SEQ ID NO: 66) in the ORF sequence.

Figure 15: alignment of IFNFH31 ORF (SEQ ID NO: 29) with pIFNFH31 protein sequence (SEQ ID NO: 30). The residues found identical in INSP037 are underlined (68% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH31_5 (forward; SEQ ID NO: 67) and CL_IFNFH31_3 (reverse; SEQ ID NO: 68) in the ORF sequence.

Figure 16: alignment of IFNFH32 ORF (SEQ ID NO: 31) with pIFNFH32 protein sequence (SEQ ID NO: 32). The residues found identical in INSP037 are underlined (70% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH32_5 (forward; SEQ ID NO: 69) and CL_IFNFH32_3 (reverse; SEQ ID NO: 70) in the ORF sequence.

Figure 17: alignment of IFNFH36 ORF (SEQ ID NO: 33) with pIFNFH36 protein sequence (SEQ ID NO: 34). The residues found identical in INSP037 are underlined (72% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH36_5 (forward; SEQ ID NO: 71) and CL_IFNFH36_3 (reverse; SEQ ID NO: 72) in the ORF sequence.

Figure 18: alignment of IFNFH37 ORF (SEQ ID NO: 35) with pIFNFH37 protein sequence (SEQ ID NO: 36). The residues found identical in INSP037 are underlined (76% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH37_5 (forward; SEQ ID NO: 73) and CL_IFNFH37_3 (reverse; SEQ ID NO: 74) in the ORF sequence.

Figure 19: alignment of IFNFH39 ORF (SEQ ID NO: 37) with pIFNFH39 protein sequence (SEQ ID NO: 38). The residues found identical in INSP037 are underlined (70% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH39_5 (forward; SEQ ID NO: 75) and CL_IFNFH39_3 (reverse; SEQ ID NO: 76) in the ORF sequence.

Figure 20: alignment of IFNFH42 ORF (SEQ ID NO: 39) with pIFNFH42 protein sequence (SEQ ID NO: 40). The residues found identical in INSP037 are underlined (67% of identity with INSP037). The arrows indicate the position of the primers CL_IFNFH42_5 (forward; SEQ ID NO: 77) and CL_IFNFH42_3 (reverse; SEQ ID NO: 78) in the ORF sequence.

Figure 21: alignment of the human IFN gamma-like INSP037 (SEQ ID NO: 155) with the protein sequences of the invention, grouped according to their length and homology. The region common to INSP037 and pIFNFHs is boxed (residues identical in INSP037 are underlined).

Figure 11: map of the expression vector pEAK12D.

DETAILED DESCRIPTION OF THE INVENTION

The main object of the present invention are novel, isolated polypeptides having at least one activity of human IFNgamma selected from the group consisting of:

a) amino acid sequences SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40;

b) variants of the amino acid sequences SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40, which are at least 80% identical to said sequences;

c) mature forms, active fragments, precursors, salts, or derivatives of the amino acid sequences given in a) or b).

The novel polypeptides pIFNFH01 (SEQ ID NO: 2), pIFNFH03 (SEQ ID NO: 4), pIFNFH04 (SEQ ID NO: 6), pIFNFH08 (SEQ ID NO: 8), pIFNFH10 (SEQ ID NO: 10), pIFNFH11 (SEQ ID NO: 12), pIFNFH12 (SEQ ID NO: 14), pIFNFH13 (SEQ ID NO: 16), pIFNFH14 (SEQ ID NO: 18), pIFNFH15 (SEQ ID NO: 20), pIFNFH20 (SEQ ID NO: 22), pIFNFH23 (SEQ ID NO: 24), pIFNFH25 (SEQ ID NO: 26), pIFNFH27 (SEQ ID NO: 28), pIFNFH31 (SEQ ID NO: 30), pIFNFH32 (SEQ ID NO: 32), pIFNFH36 (SEQ ID NO: 34), pIFNFH37 (SEQ ID NO: 36), pIFNFH39 (SEQ ID NO: 38), and pIFNFH42 (SEQ ID NO: 40) were identified on the basis of the comparable length and the sequence homology

with INSP037, a protein predicted to be an IFNgamma-like protein (GB patent application No. 0130720.6).

The totality of amino acid sequences obtained by translating the known ORFs in the human genome were challenged using INSP037 protein sequence, and the positive hits were further selected on the basis of sequence length and amino acid conservation comparable to INSP037 and/or human IFNgamma. Therefore, the novel polypeptides of the invention can be predicted to have at least one of the biological activities of human IFNgamma.

In addition to such sequences, a series of polypeptides forms part of the disclosure of the invention, such as variants of the amino acid sequences SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40, which are at least 80% identical to said sequences. Similar variants can be identified and/or designed using commonly available bioinformatic tools (Mulder NJ and Apweiler R, 2002; Rehm BH, 2001), measuring the percentage over the entire amino acid sequences disclosed in figures 1-20, or in particular over a segment of at least 78 amino acids containing the region of homology with INSP037, as indicated in figure 21. The variants may correspond to naturally occurring allelic variants of the sequences SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40, as the ones possibly resulting from the translation of a single nucleotide polymorphism.

In accordance with the present invention, any non-identical amino acid substitution should be preferably either an amino acid which is present in the same position in another of the protein sequence of the invention (figure 21), or a "conservative" or "safe" substitution, which introduces an amino acids having sufficiently similar chemical properties (eg a basic, positively charged amino acid

should be replaced by another basic, positively charged amino acid), in order to preserve the structure and the biological function of the molecule.

The literature provide many models on which the selection of conservative amino acids substitutions can be performed on the basis of statistical and physico-chemical studies on the sequence and/or the structure of proteins (Rogov SI and Nekrasov AN, 2001). Protein design experiments have shown that the use of specific subsets of amino acids can produce foldable and active proteins, helping in the classification of amino acid "synonymous" substitutions which can be more easily accommodated in protein structure, and which can be used to detect functional and structural homologs, orthologs, and paralogs (Murphy LR et al., 2000). The groups of synonymous amino acids and the groups of more preferred synonymous amino acids are shown in Table I.

Specific, non-conservative mutations can be also introduced in the polypeptides of the invention with different purposes, for example, the elimination of immunogenic epitopes, the alteration of binding properties, the alteration of the glycosylation patter n, or the improvement of protein stability (van den Burg B and Eijsink V, 2002; Robinson CR, 2002; WO 02/05146; WO 00/34317; WO 98/52976).

Mature forms, active fragments, precursors, salts, or derivatives of the amino acid sequences SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40, and of the variants defined before, are also part of the disclosure of the present invention when they have at least one of the biological activities of human IFNgamma..

Mature forms and active fragments can result from natural or artificial post-transcriptional or post-translational events. For example, truncated proteins can be generated by genetic engineering and expressed in host cells, or by a proteolytic processing leading to the removal of N-terminal sequences (by signal peptidases and

other proteolytic enzymes). Other alternative mature forms can also result from the addition of chemical groups such as sugars or phosphates.

Fragments should present deletions of terminal or internal amino acids not altering their function, and should involve generally a few amino acids, e.g., under ten, and preferably under three, without removing or displacing amino acids which are critical to the conformation of the active protein.

The "precursors" are compounds which can be converted into the compounds of present invention by metabolic and enzymatic processing prior or after the administration to the cells or to the body.

The term "salts" herein refers to both salts of carboxyl groups and to acid addition salts of amino groups of the polypeptides of the present invention. Salts of a carboxyl group may be formed by means known in the art and include inorganic salts, for example, sodium, calcium, ammonium, ferric or zinc salts, and the like, and sal ts with organic bases as those formed, for example, with amines, such as triethanolamine, arginine or lysine, piperidine, procaine and the like. Acid addition salts include, for example, salts with mineral acids such as, for example, hydrochloric acid or sulfuric acid, and salts with organic acids such as, for example, acetic acid or oxalic acid. Any of such salts should have substantially similar activity to the peptides and polypeptides of the invention or their analogs.

The term "derivatives" as herein used refers to derivatives which can be prepared from the functional groups present on the lateral chains of the amino acid moieties or on the amino- or carboxy-terminal groups according to known methods. Such molecules can result also from other modifications which do not normally alter primary sequence, for example *in vivo* or *in vitro* chemical derivativization of polypeptides (acetylation or carboxylation), those made by modifying the pattern of phosphorylation

(introduction of phosphotyrosine, phosphoserine, or phosphothreonine residues) or glycosylation (by exposing the polypeptide to mammalian glycosylating enzymes) of a peptide during its synthesis and processing or in further processing steps. Alternatively, derivatives may include esters or aliphatic amides of the carboxyl-groups and N-acyl derivatives of free amino groups or O-acyl derivatives of free hydroxyl-groups and are formed with acyl-groups as for example alcanoyl- or aryl-groups.

The generation of the derivatives may involve a site-directed modification of an appropriate residue, in an internal or terminal position. The residues used for attachment should they have a side-chain amenable for polymer attachment (i.e., the side chain of an amino acid bearing a functional group, e.g., lysine, aspartic acid, glutamic acid, cysteine, histidine, etc.). Alternatively, a residue having a side chain amenable for polymer attachment can replace an amino acid of the polypeptide, or can be added in an internal or terminal position of the polypeptide. Also, the side chains of the genetically encoded amino acids can be chemically modified for polymer attachment, or unnatural amino acids with appropriate side chain functional groups can be employed. The preferred method of attachment employs a combination of peptide synthesis and chemical ligation. Advantageously, the attachment of a water-soluble polymer will be through a biodegradable linker, especially at the amino-terminal region of a protein. Such modification acts to provide the protein in a precursor (or "pro-drug") form, that, upon degradation of the linker releases the protein without polymer modification.

Polymer attachment may be not only to the side chain of the amino acid naturally occurring in a specific position of the antagonist or to the side chain of a natural or unnatural amino acid that replaces the amino acid naturally occurring in a specific position of the antagonist, but also to a carbohydrate or other moiety that is attached to

the side chain of the amino acid at the target position. Rare or unnatural amino acids can be also introduced by expressing the protein in specifically engineered bacterial strains (Bock A, 2001).

All the above indicated variants can be natural, being identified in organisms other than humans, or artificial, being prepared by chemical synthesis, by site-directed mutagenesis techniques, or any other known technique suitable thereof, which provide a finite set of substantially corresponding mutated or shortened peptides or polypeptides which can be routinely obtained and tested by one of ordinary skill in the art using the teachings presented in the prior art.

The novel amino acid sequences disclosed in the present patent application can be used to provide different kind of reagents and molecules. Examples of these compounds are binding proteins or antibodies that can be identified using their full sequence or specific fragments, such as antigenic determinants. Peptide libraries can be used in known methods (Tribbick G, 2002) for screening and characterizing antibodies or other proteins binding the claimed amino acid sequences, and for identifying alternative forms of the polypeptides of the invention having similar binding properties.

The present patent application discloses also fusion proteins comprising any of the polypeptides described above. These polypeptides should contain protein sequence heterologous to the one disclosed in the present patent application, without significatively impairing the IFNgamma-related activity and possibly providing additional properties. Examples of such properties are an easier purification procedure, a longer lasting half-life in body fluids, an additional binding moiety, the maturation by means of an endoproteolytic digestion, or extracellular localization. This latter feature is of particular importance for defining a specific group of fusion or chimeric proteins

included in the above definition since it allows the claimed molecules to be localized in the space where not only isolation and purification of these polypeptides is facilitated, but also where generally IFNs and their receptors interact.

Design of the moieties, ligands, and linkers, as well methods and strategies for the construction, purification, detection and use of fusion proteins are disclosed in the literature (Nilsson J et al., 1997; Methods Enzymol, Vol. 326-328, Academic Press, 2000). The preferred one or more protein sequences which can be comprised in the fusion proteins belong to these protein sequences: membrane-bound protein, immunoglobulin constant region, multimerization domains, extracellular proteins, signal peptide-containing proteins, export signal-containing proteins. Features of these sequences and their specific uses are disclosed in a detailed manner, for example, for albumin fusion proteins (WO 01/77137), fusion proteins including multimerization domain (WO 01/02440, WO 00/24782), immunoconjugates (Garnett MC, 2001), or fusion protein providing additional sequences which can be used for purifying the recombinant products by affinity chromatography (Constans A, 2002; Burgess RR and Thompson NE, 2002; Lowe CR et al., 2001; J. Bioch. Biophy. Meth., vol. 49 (1-3), 2001; Sheibani N, 1999).

The polypeptides of the invention can be used to generate and characterize ligands binding specifically to them. These molecules can be natural or artificial, very different from the chemical point of view (binding proteins, antibodies, molecularly imprinted polymers), and can be produced by applying the teachings in the art (WO 02/74938; Kuroiwa Y et al., 2002; Haupt K, 2002; van Dijk MA and van de Winkel JG, 2001; Gavilondo JV and Larrick JW, 2000). Such ligands can antagonize or inhibit the IFNgamma-related activity of the polypeptide of the invention against which they have been generated. In particular, common and efficient ligands are represented by

extracellular domain of a membrane-bound protein or antibodies, which can be in the form monoclonal, polyclonal, humanized antibody, or an antigen binding fragment.

The polypeptides and the polypeptide-based derived reagents described above can be in alternative forms, according to the desired method of use and/or production, such as active conjugates or complexes with a molecule chosen amongst radioactive labels, fluorescent labels, biotin, or cytotoxic agents.

Specific molecules, such as peptide mimetics, can be also designed on the sequence and/or the structure of a polypeptide of the invention. Peptide mimetics (also called peptidomimetics) are peptides chemically modified at the level of amino acid side chains, of amino acid chirality, and/or of the peptide backbone. These alterations are intended to provide agonists or antagonists of the polypeptdes of the invention with improved preparation, potency and/or pharmacokinetics features.

For example, when the peptide is susceptible to cleavage by peptidases following injection into the subject is a problem, replacement of a particularly sensitive peptide bond with a non-cleavable peptide mimetic can provide a peptide more stable and thus more useful as a therapeutic compound. Similarly, the replacement of an L-amino acid residue is a standard way of rendering the peptide less sensitive to proteolysis, and finally more similar to organic compounds other than peptides. Also useful are amino-terminal blocking groups such as t-butyloxycarbonyl, acetyl, theyl, succinyl, methoxysuccinyl, suberyl, adipyl, azelayl, dansyl, benzyloxycarbonyl, fluorenylmethoxycarbonyl, methoxyazelayl, methoxyadipyl, methoxysuberyl, and 2,4-dinitrophenyl. Many other modifications providing increased potency, prolonged activity, easiness of purification, and/or increased half-life are disclosed in the prior art (WO 02/10195; Villain M et al., 2001).

Preferred alternative, synonymous groups for amino acids derivatives included in peptide mimetics are those defined in Table II. A non-exhaustive list of amino acid derivatives also include aminoisobutyric acid (Aib), hydroxyproline (Hyp), 1,2,3,4-tetrahydro-isoquinoline-3-COOH, indoline-2carboxylic acid, 4-difluoro-proline, L-thiazolidine-4-carboxylic acid, L-homoproline, 3,4-dehydro-proline, 3,4-dihydroxy-phenylalanine, cyclohexyl-glycine, and phenylglycine.

By "amino acid derivative" is intended an amino acid or amino acid-like chemical entity other than one of the 20 genetically encoded naturally occurring amino acids. In particular, the amino acid derivative may contain substituted or non-substituted, linear, branched, or cyclic alkyl moieties, and may include one or more heteroatoms. The amino acid derivatives can be made de novo or obtained from commercial sources (Calbiochem-Novabiochem AG, Switzerland; Bachem, USA).

Various methodologies for incorporating unnatural amino acids derivatives into proteins, using both *in vitro* and *in vivo* translation systems, to probe and/or improve protein structure and function are disclosed in the literature (Dougherty DA, 2000). Techniques for the synthesis and the development of peptide mimetics, as well as non-peptide mimetics, are also well known in the art (Goleblowski A et al., 2001; Hruby VJ and Balse PM, 2000; Sawyer TK, in "Structure Based Drug Design", edited by Veerapandian P, Marcel Dekker Inc., pg. 557-663, 1997).

Another object of the present invention are isolated nucleic acids encoding for the polypeptides of the invention having at least one activity of human IFNgamma, or the corresponding fusion proteins, as disclosed above. Preferably, these nucleic acids should comprise a DNA sequence selected from the group consisting of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35 , 37, and 39, or the complement of said DNA sequences.

Alternatively, the nucleic acids of the invention are the purified nucleic acids which hybridize under high stringency conditions, or exhibit at least about 85% identity over a stretch of at least about 30 nucleotides, with a nucleic acid selected from the group consisting of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, and 39, or a complement of said DNA sequences.

The wording "high stringency conditions" refers to conditions in a hybridization reaction that facilitate the association of very similar molecules and consist in the overnight incubation at 60-65°C in a solution comprising 50 % formamide, 5X SSC (150 m M NaCl, 15 m M trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10 % dextran sulphate, and 20 microgram/ml denatured, sheared salmon sperm DNA, followed by washing the filters in O.1X SSC at the same temperature.

These nucleic acids, including nucleotide sequences substantially the same, can be comprised in plasmids, vectors and any other DNA construct which can be used for maintaining, modifying, introducing, or expressing the encoded polypeptide in a cell or a virus. In particular, vectors wherein said nucleic acid molecule is operatively linked to expression control sequences can allow expression in prokaryotic or eukaryotic host cells of the encoded polypeptide.

The wording "nucleotide sequences substantially the same" includes all other nucleic acid sequences which, by virtue of the degeneracy of the genetic code, also code for the given amino acid sequences. In this sense, the literature provides indications on preferred or optimized codons for recombinant expression (Kane JF et al., 1995).

The nucleic acids and the vectors can be introduced into cells or virus with different purposes, generating transgenic cells and organisms. For example, a process

for producing cells capable of expressing a polypeptide of the invention comprises genetically engineering cells with such vectors or nucleic acids.

In particular, host cells (e.g. bacterial cells) can be modified by transformation for allowing the transient or stable expression of the polypeptides encoded by the nucleic acids and the vectors of the invention. Alternatively, said molecules can be used to generate transgenic animal cells or non-human organisms (by non-/homologous recombination or by any other method allowing their stable integration and expression), having enhanced or reduced expression levels of the polypeptides of the invention, when the level is compared with the normal expression levels. Such precise modifications can be obtained by making use of the nucleic acids of the inventions and of technologies associated, for example, to gene therapy (Meth. Enzymol., vol. 346, 2002) or to site-specific recombinases (Kolb AF, 2002). Model systems based on the polypeptides disclosed in the present patent application can be also generated by gene targeting into human cell lines for the systematic study of their activities (Bunz F, 2002).

The polypeptides of the invention can be prepared by any method known in the art, including recombinant DNA-related technologies, and chemical synthesis technologies. In particular, a method for making a polypeptide of the invention may comprise culturing a host or transgenic cell as described above under conditions in which the nucleic acid or vector is expressed, and recovering the polypeptide encoded by said nucleic acid or vector from cell culture. For example, when the vector expresses the polypeptide as a fusion protein with an extracellular or signal-peptide containing proteins, the recombinant product can be secreted in the extracellular space, and can be more easily collected and purified from cultured cells in view of further processing or, alternatively, the cells can be directly used or administered.

The DNA sequence coding for the proteins of the invention can be inserted and ligated into a suitable episomal or non- / homologously integrating vectors, which can be introduced in the appropriate host cells or virus by any suitable means (transformation, transfection, conjugation, protoplast fusion, electroporation, calcium phosphate-precipitation, direct microinjection, etc.). Factors of importance in selecting a particular plasmid or viral vector include: the ease with which recipient cells that contain the vector, may be recognized and selected from those recipient cells which do not contain the vector; the number of copies of the vector which are desired in a particular host; and whether it is desirable to be able to "shuttle" the vector between host cells of different species.

The vectors should allow the expression of the isolated or fusion protein including the polypeptide of the invention in the Prokaryotic or Eukaryotic host cells under the control of transcriptional initiation / termination regulatory sequences, which are chosen to be inducible or constitutively active in said cell. A cell line substantially enriched in such cells can be then isolated to provide a stable cell line.

Different transcriptional and translational regulatory sequences may be employed for Eukaryotic hosts, depending on the nature of the host (e.g. yeasts, insect, plant, or mammalian cells). They may be derived form viral sources, such as adenovirus, bovine papilloma virus, Simian virus or the like, where the regulatory signals are associated with a particular gene which has a high level of expression. Examples are the TK promoter of the Herpes virus, the SV40 early promoter, the yeast gal4 gene promoter, etc. Transcriptional initiation regulatory signals may be selected which allow for repression and activation, so that expression of the genes can be modulated. The cells stably transformed by the introduced DNA can be selected by introducing one or more markers allowing the selection of host cells which contain the expression vector. The

marker may also provide for phototrophy to an auxotropic host, resistance to biocides (e.g. antibiotics) or to heavy metals (e.g. copper). The selectable marker gene can either be directly linked to the DNA sequences to be expressed in the same vector, or introduced into the same cell by co-transfecting another vector.

Host cells may be either prokaryotic or eukaryotic. Preferred are eukaryotic hosts, e.g. mammalian cells, such as human, monkey, mouse, and Chinese Hamster Ovary (CHO) cells, because they provide post-translational modifications to proteins, including correct folding and glycosylation. Also yeast cells can carry out post-translational peptide modifications including glycosylation. A number of recombinant DNA strategies exist which utilize strong promoter sequences and high copy number of plasmids which can be utilized for production of the desired proteins in yeast. Yeast recognizes leader sequences in cloned mammalian gene products and secretes peptides bearing leader sequences (i.e., pre-peptides).

The above mentioned embodiments of the invention can be achieved by combining the disclosure provided by the present patent application on the sequence of novel polypeptides having IFNgamma-related activities with the knowledge of common molecular biology techniques.

Many books and reviews provides teachings on how to clone and produce recombinant proteins using vectors and Prokaryotic or Eukaryotic host cells, such as some titles in the series "A Practical Approach" published by Oxford University Press ("DNA Cloning 2: Expression Systems", 1995; "DNA Cloning 4: Mammalian Systems", 1996; "Protein Expression", 1999; "Protein Purification Techniques", 2001).

Moreover, literature also provides an overview of the technologies for expressing polypeptides in a high-throughput manner (Chambers SP, 2002; Coleman TA, et al., 1997), of the cell systems and the processes used industrially for the large-scale

production of recombinant proteins having therapeutic applications (Andersen DC and Krummen L, 2002, Chu L and Robinson DK, 2001), and of alternative eukaryotic expression systems for expressing the polypeptide of interest, which may have considerable potential for the economic production of the desired protein, such the ones based on transgenic plants (Giddings G, 2001) or the yeast *Pichia pastoris* (Lin Cereghino GP et al., 2002). Recombinant protein products can be rapidly monitored with various analytical technologies during purification to verify the amount and the quantity of the expressed polypeptides (Baker KN et al., 2002), as well as to check properties like bioequivalence and immunogenicity (Schellekens H, 2002; Gendel SM, 2002).

Totally synthetic proteins are disclosed in the literature (Brown A et al., 1996), and many examples of chemical synthesis technologies, which can be effectively applied for the polypeptides of the invention given their short length, are available in the literature, as solid phase or liquid phase synthesis technologies. For example, the amino acid corresponding to the carboxy-terminus of the peptide to be synthetized is bound to a support which is insoluble in organic solvents, and by alternate repetition of reactions, one wherein amino acids with their amino groups and side chain functional groups protected with appropriate protective groups are condensed one by one in order from the carboxy-terminus to the amino-terminus, and one where the amino acids bound to the resin or the protective group of the amino groups of the peptides are released, the peptide chain is thus extended in this manner. Solid phase synthesis methods are largely classified by the tBoc method and the Fmoc method, depending on the type of protective group used. Typically used protective groups include tBoc (t-butoxycarbonyl), Cl-Z (2-chlorobenzyloxycarbonyl), Br-Z (2-bromobenzyloxycarbonyl), Bzl (benzyl), Fmoc (9-fluorenylmethoxycarbonyl), Mbh (4,4'-dimethoxydibenzhydryl),

Mtr (4-methoxy-2,3,6-trimethylbenzenesulphonyl), Trt (trityl), Tos (tosyl), Z (benzyloxycarbonyl) and Cl2-Bzl (2,6-dichlorobenzyl) for the amino groups; NO2 (nitro) and Pmc (2,2,5,7,8-pentamethylchromane-6-sulphonyl) for the guanidino groups); and tBu (t-butyl) for the hydroxyl groups). After synthesis of the desired peptide, it is subjected to the de-protection reaction and cut out from the solid support. Such peptide cutting reaction may be carried with hydrogen fluoride or tri-fluoromethane sulfonic acid for the Boc method, and with TFA for the Fmoc me thod.

The purification of the polypeptides of the invention can be carried out by any one of the methods known for this purpose, i.e. any conventional procedure involving extraction, precipitation, chromatography, electrophoresis, or the like. A further purification procedure that may be used in preference for purifying the protein of the invention is affinity chromatography using monoclonal antibodies or affinity groups, which bind the target protein and which are produced and immobilized on a gel matrix contained within a column. Impure preparations containing the proteins are passed through the column. The protein will be bound to the column by heparin or by the specific antibody while the impurities will pass through. After washing, the protein is eluted from the gel by a change in pH or ionic strength. Alternatively, HPLC (High Performance Liquid Chromatography) can be used. The elution can be carried using a water-acetonitrile-based solvent commonly employed for protein purification.

The disclosure of the novel polypeptides of the invention, and the reagents disclosed in connection to them (antibodies, nucleic acids, cells) allows also to screen and characterize compounds (proteins, as well as small organic molecules) that are capable to enhance or reduce their expression level into a cell or in an animal. Examples of compounds that can reduce or block the expression of polypeptides are antisense oligonucleotides (Stein CA, 2001) or small interfering, double stranded RNA

molecules that can trigger RNA interference-mediated silencing (Paddison PJ et al., 2002; Lewis DL et al., 2002). These compounds are intended as antagonists (in addition to the ones above described in connection to mutants and ligands) in the context of the possible mechanism of antagonism for blocking cytokine/chemokine-controlled pathways as defined in the literature (Choy EH and Panayi GS, 2001; Dower SK, 2000).

"Oligonucleotides" refers to either a single stranded polydeoxynucleotide or two complementary polydeoxynucleotide strands which may be chemically synthesized. Such synthetic oligonucleotides have no 5' phosphate and thus will not ligate to another oligonucleotide without adding a phosphate with an ATP in the presence of a kinase. A synthetic oligonucleotide will ligate to a fragment that has not been dephosphorylated.

The invention includes purified preparations of the products of the invention (polypeptides, nucleic acids, cells, ligands, peptide mimetics). Purified preparations, as used herein, refers to the preparations which containing at least 1%, preferably at least 5%, by dry weight of the compounds of the invention.

The present patent application discloses a series of novel polypeptides and of related reagents having one or more human IFNgamma-related activities which can be exploited for several possible applications. In particular, whenever the increase of a human IFNgamma-related activity of a polypeptide of the invention is desirable in the therapy or in the prevention of a disease, reagents such as the disclosed INS P037-like polypeptides, the corresponding fusion proteins and peptide mimetics, the encoding nucleic acids, the expressing cells, or the compounds enhancing their expression can be used.

Therefore, the present invention discloses pharmaceutical compositions for the treatment or prevention of diseases needing an increase in a human IFNgamma activity of a polypeptide of the invention, which contain one of the disclosed INSP037-like polypeptides, the corresponding fusion proteins and peptide mimetics, the encoding nucleic acids, the expressing cells, or the compounds enhancing their expression, as active ingredient. The process for the preparation of these pharmaceutical compositions comprises combining the disclosed INSP037-like polypeptides, the corresponding fusion proteins and peptide mimetics, the encoding nucleic acids, the expressing cells, or the compounds enhancing their expression, together with a pharmaceutically acceptable carrier. Methods for the treatment or prevention of diseases needing an increase in a human IFNgamma activity of a polypeptide of the invention, comprise the administration of a therapeutically effective amount of the disclosed INSP037-like polypeptides, the corresponding fusion proteins and peptide mimetics, the encoding nucleic acids, the expressing cells, or the compounds enhancing their expression.

Amongst the novel molecules disclosed in the present patent application, the ligands or the compounds reducing the expression or the activity of polypeptides of the invention have several applications, and in particular they can be used in the therapy or in the diagnosis of a disease associated to the excessive human IFNgamma activity of a polypeptide of the invention.

Therefore, the present invention discloses pharmaceutical compositions for the treatment or prevention of diseases associated to the excessive human IFNgamma activity of a polypeptide of the invention, which contain one of the ligands or compounds reducing the expression or the activity of such polypeptides, as active ingredient. The process for the preparation of these pharmaceutical compositions

comprises combining the ligand or the compound, together with a pharmaceutically acceptable carrier. Methods for the treatment or prevention of diseases associated to the excessive IFNgamma-related activity of the polypeptide of the invention, comprise the administration of a therapeutically effective amount of the antagonist, the ligand or of the compound.

The present patent application discloses novel INSP037-like polypeptides and a series of related reagents that may be useful, as active ingredients in pharmaceutical compositions appropriately formulated, in the treatment or prevention of diseases for which a compound having a human IFNgamma-related activity may provide beneficial effects, such as cell proliferative disorders, autoimmune/inflammatory disorders, cardiovascular disorders, neurological disorders, or bacterial and viral infections. A non-exhaustive lists of disorders include multiple sclerosis, graft-vs-host disease, lymphomas, leukaemia, Crohn's disease, asthma, septic shock, type I and type II diabetes, allergies, asthma, psoriasis, inflammatory bowel disease, ulcerative colitis, fibrotic diseases, rheumatoid arthritis, and neuroblastoma.

The therapeutic applications of the polypeptides of the invention and of the related reagents can be evaluated (in terms or safety, pharmacokinetics and efficacy) by the means of the *in vivo / in vitro* assays making use of animal cell, tissues and models developed for human IFNgamma and/or IFNgamma binding proteins (Younes HM and Amsden BG, 2002; Boehm U et al., 1997; Bach EA et al., 1997), including their orthologs, or by the means of *in silico /* computational approaches (Johnson DE and Wolfgang GH, 2000), known for the validation of IFNs and other biological products during drug discovery and preclinical development.

It is intended that any disclosed use or activity related to human IFNgamma (or its orthologs) disclosed in the prior art is also applicable to any corresponding

embodiment of the present invention, such as therapeutic uses and compositions, alone or in combination with another compounds (EP311616, WO 01/34180, EP 490250, EP203580, EP502997, EP886527, EP696639), formulations (EP697887, WO 01/36001), expression systems (WO 01/57218) known for human IFNgamma.

The pharmaceutical compositions of the invention may contain, in addition to INSP037-like polypeptide or to the related reagent, suitable pharmaceutically acceptable carriers, biologically compatible vehicles and additives which are suitable for administration to an animal (for example, physiological saline) and eventually comprising auxiliaries (like excipients, stabilizers, adjuvants, or diluents) which facilitate the processing of the active compound into preparations which can be used pharmaceutically.

The pharmaceutical compositions may be formulated in any acceptable way to meet the needs of the mode of administration. For example, of biomaterials, sugar-macromolecule conjugates, hydrogels, polyethylene glycol and other natural or synthetic polymers can be used for improving the active ingredients in terms of drug delivery efficacy. Technologies and models to validate a specific mode of administration are disclosed in literature (Davis BG and Robinson MA, 2002; Gupta P et al., 2002; Luo B and Prestwich GD, 2001; Cleland JL et al., 2001; Pillai O and Panchagnula R, 2001).

Polymers suitable for these purposes are biocompatible, namely, they are non-toxic to biological systems, and many such polymers are known. Such polymers may be hydrophobic or hydrophilic in nature, biodegradable, non-biodegradable, or a combination thereof. These polymers include natural polymers (such as collagen, gelatin, cellulose, hyaluronic acid), as well as synthetic polymers (such as polyesters, polyorthoesters, polyanhydrides). Examples of hydrophobic non-degradable polymers

include polydimethyl siloxanes, polyurethanes, polytetrafluoroethylenes, polyethylenes, polyvinyl chlorides, and polymethyl methaerylates. Examples of hydrophilic non-degradable polymers include poly(2-hydroxyethyl methacrylate), polyvinyl alcohol, poly(N-vinyl pyrrolidone), polyalkylenes, polyacrylamide, and copolymers thereof. Preferred polymers comprise as a sequential repeat unit ethylene oxide, such as polyethylene glycol (PEG).

Any accepted mode of administration can be used and determined by those skilled in the art to establish the desired blood levels of the active ingredients. For example, administration may be by various parenteral routes such as subcutaneous, intravenous, intradermal, intramuscular, intraperitoneal, intranasal, transdermal, oral, or buccal routes. The pharmaceutical compositions of the present invention can also be administered in sustained or controlled release dosage forms, including depot injections, osmotic pumps, and the like, for the prolonged administration of the polypeptide at a predetermined rate, preferably in unit dosage forms suitable for single administration of precise dosages.

Parenteral administration can be by bolus injection or by gradual perfusion over time. Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions, which may contain auxiliary agents or excipients known in the art, and can be prepared according to routine methods. In addition, suspension of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides. Aqueous injection suspensions that may contain substances increasing the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran.

Optionally, the suspension may also contain stabilizers. Pharmaceutical compositions include suitable solutions for administration by injection, and contain from about 0.01 to 99.99 percent, preferably from about 20 to 75 percent of active compound together with the excipient.

The wording "therapeutically effective amount" refers to an amount of the active ingredients that is sufficient to affect the course and the severity of the disease, leading to the reduction or remission of such pathology. The effective amount will depend on the route of administration and the condition of the patient.

The wording "pharmaceutically acceptable" is meant to encompass any carrier, which does not interfere with the effectiveness of the biological activity of the active ingredient and that is not toxic to the host to which is administered. For example, for parenteral administration, the above active ingredients may be formulated in unit dosage form for injection in vehicles such as saline, dextrose solution, serum albumin and Ringer's solution. Carriers can be selected also from starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the various oils, including those of petroleum, animal, vegetable or synthetic origin (peanut oil, soybean oil, mineral oil, sesame oil).

It is understood that the dosage administered will be dependent upon the age, sex, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. The dosage will be tailored to the individual subject, as is understood and determinable by one of skill in the art. The total dose required for each treatment may be administered by multiple doses or in a single dose. The pharmaceutical composition of the present invention may be administered

alone or in conjunction with other therapeutics directed to the condition, or directed to other symptoms of the condition. Usually a daily dosage of active ingredient is comprised between 0.01 to 100 milligrams per kilogram of body weight per day. Ordinarily 1 to 40 milligrams per kilogram per day given in divided doses or in sustained release form is effective to obtain the desired results. Second or subsequent administrations can be performed at a dosage, which is the same, less than, or greater than the initial or previous dose administered to the individual.

Apart from the methods having a therapeutic or a production purpose, several other methods can make use of the INSP037-like polypeptides and of the related reagents disclosed in the present patent application.

In a first example, a method for screening candidate compounds effective to treat a disease related to a INSP037-like polypeptides of the invention, comprises:

(a) contacting host cells expressing such polypeptide, transgenic non-human animals, or transgenic animal cells having enhanced or reduced expression levels of the polypeptide, with a candidate compound and

(b) determining the effect of the compound on the animal or on the cell.

In a second example, a method for identifying a candidate compound as an antagonist/inhibitor or agonist/activator of a polypeptide of the invention comprises:

(a) contacting the polypeptide, the compound, and a mammalian cell or a mammallian cell membrane; and

(b) measuring whether the molecule blocks or enhances the interaction of the polypeptide, or the response that results from such interaction, with the mammalian cell or the mammalian cell membrane.

In a third example, methods for determining the activity and/or the presence of the polypeptide of the invention in a sample, can detect either the polypeptide or the encoding RNA/DNA. Thus, such a method comprises:

(a) providing a protein-containing sample;

(b) contacting said sample with a ligand of the invention; and

(c) determining the presence of said ligand bound to said polypeptide, thereby determining the activity and/or the presence of polypeptide in said sample.

Alternatively, the method comprises:

(a) providing a nucleic acids-containing sample;

(b) contacting said sample with a nucleic acid of the invention; and

(c) determining the hybridization of said nucleic acid with a nucleic acid into the sample, thereby determining the presence of the nucleic acid in the sample.

In this sense, primer sequences containing the sequences SEQ ID NO: 41-78 (Table III) can be used as well for determining the presence or the amount of a transcript or of a nucleic acid encoding a polypeptide of invention in a sample by means of Polymerase Chain Reaction amplification.

A further object of the present invention are kits for measuring the activity and/or the presence of INSP037-like polypeptide of the invention in a sample comprising one or more of the reagents disclosed in the present patent application: a INSP037-like polypeptide of the invention, a ligand, a peptide mimetic, an isolated nucleic acid or vector, a pharmaceutical composition, an expressing cell, a compound increasing or decreasing the expression levels, and/or primer sequences containing any of the sequences SEQ ID NO: 41-78.

Those kits can be used for *in vitro* diagnostic or screenings methods, and their actual composition should be adapted to the specific format of the sample (e.g.

biological sample tissue from a patient), and the molecular species to be measured. For example, if it is desired to measure the concentration of the INSP037-like polypeptide, the kit may contain an antibody and the corresponding protein in a purified form to compare the signal obtained in Western blot. Alternatively, if it is desired to measure the concentration of the transcript for the INSP037-likepolypeptide, the kit may contain a specific nucleic acid probe designed on the corresponding ORF sequence, or may be in the form of nucleic acid array containing such probe, or the primer sequences disclosed as SEQ ID NO: 41-78 (Table III). The kits can be also in the form of protein-, peptide mimetic-, or cell-based microarrays (Templin MF et al., 2002; Pellois JP et al., 2002; Blagoev B and Pandey A, 2001), allowing high-throughput proteomics studies, by making use of the proteins, peptide mimetics and cells disclosed in the present patent application.

All publications, patents and patent applications cited herein are incorporated in full by reference for any purpose.

The invention will now be described with reference to the specific embodiments by means of the following Examples, which should not be construed as in any way limiting the present invention. The content of the description comprises all modifications and substitutions which can be practiced by a person skilled in the art in light of the above teachings and, therefore, without extending beyond the meaning and purpose of the claims.

EXAMPLES

Example 1: Selection of open reading frames (ORFs) encoding for polypeptides homologous to INSP037

INSP037 was identified as an IFNgamma-like protein encoded by an ORF in human genome (GB patent application No. 0130720.6). The sequence of this ORF was used to search for homologous ORFs in human genome (Celera and GenBank databases). The homology was detected using the BLAST (Basic Local Alignment Search Tool; NCBI version 2), an algorithm which generates local alignments between a query and a hit sequence (Gish W and States DJ, 1993; Pearson WR and Miller W, 1992; Altschul SF et al., 1990). In this case the TBLASTN algorithm was used with the INSP037 protein sequence as a query. TBLASTN compares the query sequence to the database translated into 6 frames and can therefore identify a protein match to a DNA sequence in any reading frame. BLAST parameters used were: Comparison matrix = BLOSUM62; word length = 3; .E value cutoff = 10; Gap opening and extension = default; No filter.

The pattern of the homologous regions were extracted from the BLAST output file using a script written in PERL (Practical Extraction and Report Language), a programming language having powerful pattern matching functions into large text data files allowing the extraction of information from genomic DNA sequences, starting from an alpha-numerical expression describing a defined consensus sequence (Stein LD, 2001). Another PERL script was used to retrieve the entire ORFs having such INSP037-like features, extending the sequence 5' to the first potential start methionine and 3' to the first stop codon.

A total of 20 ORFs out of the 93 hits matching the original query generated on the basis of INSP037 protein sequence were selected since they have a start Methionine and a stop codon separated by between 75 and 150 codons. IFNFHs selected DNA

sequences (SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35 , 37, and 39), belong to different human chromosomes, potentially encode for protein sequences (SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40) having a significant homology with INSP037 (BLAST E value minor or equal to $7e^{-23}$), with level of identity comprised between 67% and 78.5% (figures 1-20). The novelty of the protein sequences was assessed by searching protein databases (SwissProt/Trembl and Derwent GENESEQ) using BLAST.

Amongst these sequences characterized as novel INSP037-like polypeptides, three of them (pIFNFH04, pIFNFH32, and pIFNFH20) are less than 10% longer than INSP037, while all the other sequences more than 10% longer due to an extended C-terminal region (pIFNFH08, pIFNFH12, pIFNFH25, pIFNFH36, pIFNFH37, pIFNFH23, pIFNFH27, pIFNFH14, pIFNFH01, pIFNFH10, pIFNFH11, pIFNFH13, pIFNFH31, pIFNFH03, and pIFNFH15), or to extended N-terminal and C-terminal regions (pIFNFH39 and pIFNFH42). The extended C-terminal regions present some significant local homologies amongst the different IFNFHs (figure 21). Even if not directly identified in figures 1-20, at least some of the selected polypeptides contain a functional signal peptide (Example 3).

Example 2: Cloning of the novel INSP037-like ORFs from human genomic DNA

The selected IFNFH sequences (with the exception of IFNFH25) were cloned from human genomic DNA into a cloning vector, and then transferred into an expression vector using Polymerase Chain Reaction (PCR), with pairs of forward/reverse primers specific for each ORF (see arrows in figures 1-12 and 14-20).

The cloning primers (CL series; SEQ ID NO: 41-78, Table III), containing from 21 to 30 nucleotides, were designed for amplifying each ORF using human genomic DNA

as template, since all ORFs are uninterrupted on human chromosomes. The forward primers start from three nucleotides before initial ATG. The reverse primers are complementary to the 3' end of the ORF, including the stop codon. Being the N-terminal sequences very similar amongst the different IFNFHs, the reverse primers actually are actually responsible for the specificity of the amplification reaction.

The PCR was performed by mixing the following components in each ORF-specific reaction (total volume of 50 µl in double-distilled water):

150 ng human genomic DNA (Clontech)

1.2 µM primers (0.6 µM each primer)

240 µM dNTP (Invitrogen)

0.5 µl AmpliTaq (2.5 Units; Applied Biosystems)

5 AmpliTaq buffer 10X (Applied Biosystems)

The PCR reactions were performed using an initial denaturing step if 94 ^{0}C for 2 minutes, followed by 30 cycles:

94^{0}C for 30 seconds

55^{0}C for 30 seconds

72^{0}C for 30 seconds

After a final elongation step of 72^{0}C for 10 minutes, the PCR products were directly subcloned into the pCRII-TOPO vector using the TOPO™ cloning system (Invitrogen), according to manufacturer's standard protocol. The TOPO cloning system is a variation of the TA cloning system allowing the rapid cloning of PCR products, taking advantage from the fact that Taq polymerase leaves a single Adenosine at the 3' end of PCR products. Since the TOPO vector has single-stranded Thymine overhangs, Topoisomerase I enzyme is able to join the T-ends of the vector to the A-overhangs of the PCR product, which can be used without any purification step.

The resulting plasmids (pCRTOPO-ORF series) were used to transform *E. coli* cells (TOP10F', Invitrogen, supplied with the TOPO TA Cloning Kit), obtaining several clones for each ORF. Plasmid DNA was isolated using a commercial kit (WIZARD Plasmid Minipreps: Promega) and sequenced to verify the identity of the amplified and cloned sequence with the originally selected human genomic DNA sequence.

The plasmids containing the desired sequences were used in a further round of PCR reactions necessary for transferring the ORFs into the expression vector pEAK12D (figure 22), which allows the expression of the cloned insert under the control of EF-1α promoter and in frame with a 6-His Tag sequence, using the Gateway cloning system (Invitrogen).

The expression vector pEAK12D was constructed by modifying pEAK12 (Edge Biosystems). This vector was digested with HindIII and NotI, made blunt ended with Klenow and dephosphorylated using calf-intestinal alkaline phosphatase. After dephosphorylation, the vector was ligated to blunt ended Gateway reading frame cassette C (Gateway vector conversion system, Invitrogen cat no. 11828-019) which contains AttR recombination sites flanking the ccdB gene (marker for negative selction of non-recombinant plasmids) and chloramphenicol resistance. The resulting plasmids were used to transform DB3.1 *E. coli* cells, which allow propagation of vectors containing the ccdB gene. Miniprep DNA was isolated from several of the resultant colonies and digested with AseI / EcoRI to identify clones yielding a 670 bp fragment, obtainable only when the cassette had been inserted in the correct orientation. The resultant plasmid was called pEAK12D.

Two series of primers were designed to add the ATTB1 and ATTB2 recombination sites (necessary for the integration in the expression vector) at the 5' and 3' end, respectively, of the ORF-containing insert. In the first series of primers

(EX1 series; SEQ ID NO: 79-116, Table IV), the original ORF-specific CL primers were modified by adding, at the 5' end, the sequence AAGCAGGCTTCGCCACC (for forward primers) or GTGATGGTGATGGTG (for reverse primers, but after eliminating the nucleotides complementary to the stop codon). In the second series of primers (EX2 series; SEQ ID NO: 117-154, Table V), the original ORF-specific CL primers were modified by adding, at the 5' end, the sequence GGGGACAAGTTTGTACAAAAAAGC AGGCTTCGCCACC (for forward primers) or GGGGACCACTTTGTACAAGAAAGCTG GGTTTCAATGGTGATGGTGATGGTG (for reverse primers, but after eliminating the nucleotides complementary to the stop codon). These reverse primers contain the codons for the 6-His tag which result fused in frame with the ORFs at their C-terminal end.

The PCR amplification was performed in 2 consecutive reactions. The first one was performed by mixing the following components (total volume 50 µl in double-distilled water):

25 ng pCRTOPO-ORF vector

5mM dNTP (Invitrogen)

0.5 µl Pfx DNA polymerase (Invitrogen)

0.5 µl each EX1 primer (100µM)

5µl 10X Pfx polymerase buffer(Invitrogen)

The PCR reactions were performed using an initial denaturing step of 95^{0}C for 2 minutes, followed by 10 cycles:

94^{0}C for 15 seconds

68^{0}C for 30 seconds

The PCR products were purified using the Wizard PCR prep DNA purification system (Promega), and added as templates in a second PCR reaction including the following components (total volume 50 µl in double-distilled water):

10 µl purified PCR product

5mM dNTP (Invitrogen)

0.5 µl Pfx DNA polymerase (Invitrogen)

0.5 µl each EX2 primer (100µM)

5µl 10X Pfx polymerase buffer (Invitrogen)

The PCR reactions were performed an initial denaturing step of 95°C for 1 minute, followed by 4 cycles:

94°C for 15 seconds

50°C for 30 seconds

68°C for 3 minutes 30 seconds

Then the following conditions were applied for 25 cycles:

94°C for 15 seconds

55°C for 30 seconds

68°C for 3 minutes 30 seconds.

The DNA fragments resulting from the PCR reactions were purified as described before and recombined into the pEAK12D vector using the Gateway system.

First, the following 10 µl reactions were assembled:

pDONR-201 (0.1 µg/µl)	1.5 µl
PCR product	5 µl
BP buffer	2 µl
BP enzyme mix	1.5 µl

After being incubated at room temperature for 1 hour, the reaction was stopped by adding proteinase K (1 µl, 2 µg) and incubating at 37 °C for further 10 minutes.

An aliquot of this reaction (2 µl) was used for transforming *E. coli* cells (strain DH10B) by electroporation. Plasmid DNA was prepared for 4 clones for each ORF and used for parallel 10 µl recombination reactions containing:

pEAK12D (0.1 µg / µl)	1.5 µl
Plasmid DNA	1.5 µl
ddH20	3.5 µl
LR buffer	2 µl
LR enzyme mix	1.5 µl

After being incubated at room temperature for 1 hour, the reaction was stopped by adding proteinase K (1 µl, 2 µg) and incubating at 37°C for further 10 minutes. An aliquot of this reaction (1 µl) was used for transforming DH10B *E. coli* cells by electroporation. The clones containing the correct insert were identified first by performing colony PCR on 3 colonies using the forward and reverse vector primers pEAK12D F1 (GCCAGCTTGGCACTTGATGT) and pEAK12D R1 (GATGGAGGTGGA CGTGTCAG), then confirmed by sequencing the insert with the same primer.

Example 3: Expression and purification of the His-tagged INSP037-like polypeptides in Mammalian cells

The vectors generated in Example 2 were used to express pIFNFHs in Human Embryonic Kidney cells expressing the Epstein-Barr virus Nuclear Antigen (cell line HEK293-EBNA).

The cells were seeded in T225 flasks (50 ml at a density of $2x10^5$ cells/ml) from 16 to 20 hours prior to transfection, which was performed using the cationic polymer

reagent JetPEI™ (PolyPlus-transfection; 2 µl/µg of plasmid DNA). For each flask, 113 µg of the ORF-specific pEAK12D plasmid, which were prepared using CsCl (Sambrook, J et al. "Molecular Cloning, a laboratory manual"; 2nd edition. 1989; Cold Spring Harbor Laboratory Press), were co-transfected with 2.3 µg of a plasmid acting as positive control since it expresses Green Fluorescent Protein (GFP) in a constitutive manner. The plasmids, diluted in 230 µl of JetPEI™ solution, were added to 4.6 ml of NaCl 150 mM, vortexed and incubated for 30 minutes at room temperature. This transfection mix was then added to the T225 flask and incubated at 37 °C for 6 days. An aliquot of the cultures was then exposed to UV irradiation to check the transfection efficiency by evaluating GFP fluorescence.

Culture medium from HEK293-EBNA cells transfected with the ORF-specific pEAK12D plasmids were pooled and 100 ml of the medium were diluted to 200 ml with 100 ml of ice-cold buffer A (50 mM NaH_2PO_4; 600 mM NaCl; 8.7 % (w/v) glycerol, pH 7.5), which is the same buffer used for equilibrating the affinity column on which His-tagged proteins were subsequently immobilized and eluted. The solution was filtered through a 0.22 µm sterile filter (Millipore) and kept at 4°C in 250 ml sterile square media bottles until further processing.

Two consecutive chromatography procedures were applied to the samples using an HPLC-based system (Perfusion Chromatography™, PerSeptive Biosystems) including a VISION workstation (BioCAD™ series), POROS™ chromatographic media, and an external 250 ml-sample loader (Labomatic), all kept at 4°C.

In the first chromatography step, a Ni-metal affinity column (0.83 ml, POROS 20 MC) was first regenerated with 30 column volumes of EDTA solution (100 mM EDTA; 1 M NaCl; pH 8.0), and then recharged with Ni ions through washing with 15 column volumes of the Ni solution (100 mM $NiSO_4$). The column is subsequently washed with

10 column volumes of buffer A, 7 column volumes of buffer B (50 mM NaH_2PO_4; 600 mM NaCl; 8.7 % (w/v) glycerol, 400 mM; Imidazole, pH 7.5), and finally equilibrated with 15 column volumes of buffer A containing 15 mM imidazole. The sample loader charged the protein-containing solution onto the Ni metal affinity column at a flow rate of 10 ml/min. The column was then washed with 12 column volumes of Buffer A, followed by 28 column volumes of Buffer A containing a concentration of imidazole (20 mM) allowing the elution of contaminating proteins that are loosely attached to the Ni-column. The His-tagged protein is finally eluted with 10 column volumes of Buffer B at a flow rate of 2 ml/min, collecting collected 1.6 ml fractions.

In the second chromatography step, a gel-filtration column (10 ml G-25 Sephadex) was regenerated with 2 ml of buffer D (137 mM NaCl; 2.7 mM KCl; 1.5 mM KH_2PO_4; 8 mM Na_2HPO_4; 1 M NaCl; pH 7.2), and then equilibrated with 2 column volumes of buffer C (137 mM NaCl; 2.7 mM KCl; 1.5 mM KH_2PO_4; 8 mM Na_2HPO_4; 20 % (w/v) glycerol; pH 7.4) before injecting the Ni-column peak fractions onto this column. The sample is eluted with buffer C and the desalted sample is recovered in 2.2 ml fractions.

The peak fractions from the gel-filtration column were then analyzed for their protein content using SDS-PAGE and the parallel detection by Coomassie staining and by Western blot with antibodies recognizing His-tags.

The fractions were filtered through a 0.22 µm sterile centrifugation filter (Millipore) and allquots (20 µl) were analyzed on SDS-PAGE (4-12 % NuPAGE gel; Novex). Protein concentrations were determined in the samples that show detectable protein bands by Coomassie staining, using the BCA Protein Assay kit (Pierce) and Bovine Serum Albumin as standard. The gel for the Western blot analysis was electrotransferred to a nitrocellulose membrane at 290 mA at 4°C for 1 hour. The

membrane was blocked with 5 % milk powder in PBS (137 mM NaCl; 2.7 mM KCl; 1.5 mM KH_2PO_4; 8 mM Na_2HPO_4;pH 7.4), and subsequently incubated with a mixture of 2 rabbit polyclonal anti-His antibodies (G-18 and H-15, 0.2 µg/ml each; Santa Cruz) at 4°C overnight. After a further 1 hour incubation at room temperature, the membrane was washed with PBS containing 0.1% Tween-20 (3 x 10 min), and then exposed to a secondary Horse-Radish Peroxidase (HRP)-conjugated anti-rabbit antibody (DAKO) at room temperature for 2 hours. After washing in PBS containing 0.1% Tween-20 (3 x 10 minutes), the ECL kit (Amersham Pharmacia) was used to detect the antibodies immobilized onto the membrane, comparing the film with the image of the Coomassie stained gel.

By making use of the above described protocol of protein expression and purification, the presence of sequences allowing secretion into the protein sequences encoded from the cloned ORFs was demonstrated for pIFNFH15, pIFNFH23, pIFNFH32, and pIFNFH42, which were efficiently purified from the culture medium of the transfected mammalian cells as His-tagged proteins.

Example 4: Cell- and Animal-based assay for the validation and characterization of the INSP037-like polypeptides.

Several assays have been developed for testing specificity, potency, and efficacy of IFNgamma using cell cultures or animal models, as extensively reviewed (Younes HM and Amsden BG, 2002; Boehm U et al., 1997). Other examples of literature providing examples of human IFNgamma activities are the patent applications disclosing IFNgamma variants (WO 02/81507) or the several therapeutic activities of IFNgamma, alone or in combination with other compounds (WO 95/22328, WO 01/34180, WO 90/03189, EP607258, EP696639, EP490250, EP502997). This prior art

provides reliable guidance on how to identify any human IFNgamma activity of the polypeptides of the invention.

Many assays and technologies for generating useful tools and products (antibodies, transgenic animals, radiolabeled proteins, etc.) have been also described in connection to human IFNgamma and/or its receptor (Aral C et al., 1999; Dow SW et al., 1999; Akbar S et al., 1999; Popko B and Baerwald KD, 1999; Zanti N et al., 1998; Sethi SK et al., 1997; Young HA, 1997; Bach EA et al., 1997). They can be used to verify the expression and the mechanisms of action of the polypeptides of the invention homologous to INSP037 and related reagents, in connection with possible therapeutic or diagnostic methods and uses.

TABLE I

Amino Acid	Synonymous Groups	More Preferred Synonymous Groups
Ser	Gly, Ala, Ser, Thr, Pro	Thr, Ser
Arg	Asn, Lys, Gln, Arg, His	Arg, Lys, His
Leu	Phe, Ile, Val, Leu, Met	Ile, Val, Leu, Met
Pro	Gly, Ala, Ser, Thr, Pro	Pro
Thr	Gly, Ala, Ser, Thr, Pro	Thr, Ser
Ala	Gly, Thr, Pro, Ala, Ser	Gly, Ala
Val	Met, Phe, Ile, Leu, Val	Met, Ile, Val, Leu
Gly	Ala, Thr, Pro, Ser, Gly	Gly, Ala
Ile	Phe, Ile, Val, Leu, Met	Ile, Val, Leu, Met
Phe	Trp, Phe,Tyr	Tyr, Phe
Tyr	Trp, Phe,Tyr	Phe, Tyr
Cys	Ser, Thr, Cys	Cys
His	Asn, Lys, Gln, Arg, His	Arg, Lys, His
Gln	Glu, Asn, Asp, Gln	Asn, Gln
Asn	Glu, Asn, Asp, Gln	Asn, Gln
Lys	Asn, Lys, Gln, Arg, His	Arg, Lys, His
Asp	Glu, Asn, Asp, Gln	Asp, Glu
Glu	Glu, Asn, Asp, Gln	Asp, Glu
Met	Phe, Ile, Val, Leu, Met	Ile, Val, Leu, Met
Trp	Trp, Phe,Tyr	Trp

TABLE II

Amino Acid	Synonymous Groups
Ser	D-Ser, Thr, D-Thr, allo-Thr, Met, D-Met, Met(O), D-Met(O), L-Cys, D-Cys
Arg	D-Arg, Lys, D-Lys, homo-Arg, D-homo-Arg, Met, Ile, D-.Met, D-Ile, Orn, D-Om
Leu	D-Leu, Val, D-Val, AdaA, AdaG, Leu, D-Leu, Met, D-Met
Pro	D-Pro, L-l-thioazolidine-4-carboxylic acid, D-or L-1-oxazolidine-4-carboxylic acid
Thr	D-Thr, Ser, D-Ser, allo-Thr, Met,D-Met, Met(O), D-Met(O), Val, D-Val
Ala	D-Ala, Gly, Aib, B-Ala, Acp, L-Cys, D-Cys
Val	D-Val, Leu, D-Leu, Ile, D-Ile, Met, D-Met, AdaA, AdaG
Gly	Ala, D-Ala, Pro, D-Pro, Aib, .beta.-Ala, Acp
Ile	D-Ile, Val, D-Val, AdaA, AdaG, Leu, D-Leu, Met, D-Met
Phe	D-Phe, Tyr, D-Thr, L-Dopa, His, D-His, Trp, D-Trp, Trans-3,4, or 5-phenylproline, AdaA, AdaG, cis-3,4, or 5-phenylproline, Bpa, D-Bpa
Tyr	D-Tyr, Phe, D-Phe, L-Dopa, His, D-His
Cys	D-Cys, S–Me–Cys, Met, D-Met, Thr, D-Thr
Gln	D-Gln, Asn, D-Asn, Glu, D-Glu, Asp, D-Asp
Asn	D-Asn, Asp, D-Asp, Glu, D-Glu, Gln, D-Gln
Lys	D-Lys, Arg, D-Arg, homo-Arg, D-homo-Arg, Met, D-Met, Ile, D-Ile, Om, D-Orn
Asp	D-Asp, D-Asn, Asn, Glu, D-Glu, Gln, D-Gln
Glu	D-Glu, D-Asp, Asp, Asn, D-Asn, Gln, D-Gln
Met	D-Met, S–Me--Cys, Ile, D-Ile, Leu, D-Leu, Val, D-Val

TABLE III

SEQ ID NO:	NAME	DIRECTION	5'-3' SEQUENCE
41	CL_IFNFH01_5	Forward	AACATGACCTCACCAAATAAAC
42	CL_IFNFH01_3	Reverse	TCATTTTTTTTTATTCCTTTTCTTTTGTC
43	CL_IFNFH03_5	Forward	AACATGACATCACCAAATGAG
44	CL_IFNFH03_3	Reverse	TTACAGGTGCCTGCCACTGCAC
45	CL_IFNFH04_5	Forward	AACATGACCTCACCAAATGAAC
46	CL_IFNFH04_3	Reverse	TCAAGAGACTGATGCATTCTTTAG
47	CL_IFNFH08_5	Forward	AACATGACCTCACCAAATGAAC
48	CL_IFNFH08_3	Reverse	CTAATTCCGATTAATTCTACTATG
49	CL_IFNFH10_5	Forward	AACATGACCTCACCAAATGAG
50	CL_IFNFH10_3	Reverse	TCATTGTTTTTTGTTGTTTTTGGTC
51	CL_IFNFH11_5	Forward	CACATGACCTCAGGAAATGA AG
52	CL_IFNFH11_3	Reverse	TTATTGTTTTTTATTCTTTTTCTTTTG
53	CL_IFNFH12_5	Forward	AACATGACCTCACCAAATGAAC
54	CL_IFNFH12_3	Reverse	TCAATCAGTTCTGCTATTAAAAAACTC
55	CL_IFNFH13_5	Forward	AACATGACCTCACCAAATGAAC
56	CL_IFNFH13_3	Reverse	TTAGGTGTGCTTCATTCTTTTATATT TTTT
57	CL_IFNFH14_5	Forward	AACATGACATCAACAAAGGAAC
58	CL_IFNFH14_3	Reverse	TTATATTCTTTTTTCTCTTCTGACTG
59	CL_IFNFH15_5	Forward	AATATGACCTCACCAAATGAAC
60	CL_IFNFH15_3	Reverse	CTATTTAAGGCCAATAACTTTTAG
61	CL_IFNFH20_5	Forward	AACATGCCCTTACCAAATGAGC
62	CL_IFNFH20_3	Reverse	CTATGATGCATTCTTCATTATAC
63	CL_IFNFH23_5	Forward	AACATGACCTCACCAAATGAAC
64	CL_IFNFH23_3	Reverse	CTATATACTTTCAAATAGCCTGTC
65	CL_IFNFH27_5	Forward	AACATGACCTCGCCTAATGAAC
66	CL_IFNFH27_3	Reverse	TTAGTTTGCTTCCTCTGACTG
67	CL_IFNFH31_5	Forward	AATATGACCTCACCAAATGAAC
68	CL_IFNFH31_3	Reverse	CTAATACATGCTTCTTTTTTTGTTTG
69	CL_IFNFH32_5	Forward	AACATGACCTCACCAAATAAAC
70	CL_IFNFH32_3	Reverse	TCAGTATGCCAGTTGATTTTTCAGC
71	CL_IFNFH36_5	Forward	AACATGACCTCACCAAACAAAC
72	CL_IFNFH36_3	Reverse	TTATTCTGCTTGCTCAATTCTGC
73	CL_IFNFH37_5	Forward	AACATGACCTCACTAAATGAAC
74	CL_IFNFH37_3	Reverse	CTAATTCTTTTTTTCTGCTCCATAAATTC
75	CL_IFNFH39_5	Forward	TCAATGGCCAGACACCTACAAAC
76	CL_IFNFH39_3	Reverse	TCATTCTTCTACTTGATTAATTCTAC
77	CL_IFNFH42_5	Forward	TCAATGCCAAGACACCAAAGAAC
78	CL_IFNFH42_3	Reverse	CTAATTCTTCTTTTCTACTCGATCC

TABLE IV

SEQ ID NO:	NAME	DIRECTION	5'-3' SEQUENCE
79	EX1_IFNFH01_5	Forward	AAGCAGGCTTCGCCACC AACATGACCTCACCAAATAAAC
80	EX1_IFNFH01_3	Reverse	GTGATGGTGATGGTG TTTTTTTTTATTCCTTTTCTTTTGTC
81	EX1_IFNFH03_5	Forward	AAGCAGGCTTCGCCACC AACATGACATCACCAAATGAG
82	EX1_IFNFH03_3	Reverse	GTGATGGTGATGGTG CAGGTGCCTGCCACTGCAC
83	EX1_IFNFH04_5	Forward	AAGCAGGCTTCGCCACC ATGACCTCACCAAATGAAC
84	EX1_IFNFH04_3	Reverse	GTGATGGTGATGGTG AGAGACTGATGCATTCTTTAG
85	EX1_IFNFH08_5	Forward	AAGCAGGCTTCGCCACC AACATGACCTCACCAAATGAAC
86	EX1_IFNFH08_3	Reverse	GTGATGGTGATGGTG ATTCCGATTAATTCTACTATG
87	EX1_IFNFH10_5	Forward	AAGCAGGCTTCGCCACC AACATGACCTCACCAAATGAG
88	EX1_IFNFH10_3	Reverse	GTGATGGTGATGGTG TTGTTTTTTGTTGTTTTTGGTC
89	EX1_IFNFH11_5	Forward	AAGCAGGCTTCGCCACC CACATGACCTCAGGAAATGAAG
90	EX1_IFNFH11_3	Reverse	GTGATGGTGATGGTG TTGTTTTTTATTCTTTTTCTTTTG
91	EX1_IFNFH12_5	Forward	AAGCAGGCTTCGCCACC AACATGACCTCACCAAATGAAC
92	EX1_IFNFH12_3	Reverse	GTGATGGTGATGGTG ATCAGTTCTGCTATTAAAA AACTC
93	EX1_IFNFH13_5	Forward	AAGCAGGCTTCGCCACC AACATGACCTCACCAAATGAAC
94	EX1_IFNFH13_3	Reverse	GTGATGGTGATGGTG GGTGTGCTTCATTCTTTTATATTTTTT
95	EX1_IFNFH14_5	Forward	AAGCAGGCTTCGCCACC AACATGACATCAACAAAGGAAC
96	EX1_IFNFH14_3	Reverse	GTGATGGTGATGGTG TATTCTTT TTTCTCTTCTGACTG
97	EX1_IFNFH15_5	Forward	AAGCAGGCTTCGCCACC AATATGACCTCACCAAATGAAC
98	EX1_IFNFH15_3	Reverse	GTGATGGTGATGGTG TTTAAGGCCAATAACTTTTAG
99	EX1_IFNFH20_5	Forward	AAGCAGGCTTCGCCACC AACATGCCCTTACCAAATGAGC
100	EX1_IFNFH20_3	Reverse	GTGATGGTGATGGTG TGATGCATTCTTCATTATAC
101	EX1_IFNFH23_5	Forward	AAGCAGGCTTCGCCACC AACATGACCTCACCAAATGAAC
102	EX1_IFNFH23_3	Reverse	GTGATGGTGATGGTG TATACTTTCAAATAGCCTGTC
103	EX1_IFNFH27_5	Forward	AAGCAGGCTTCGCCACC AACATGACCTCGCCTAATGAAC
104	EX1_IFNFH27_3	Reverse	GTGATGGTGATGG TGGTTTGCTTCCTCTGACTG
105	EX1_IFNFH31_5	Forward	AAGCAGGCTTCGCCACC AATATGACCTCACCAAATGAAC
106	EX1_IFNFH31_3	Reverse	GTGATGGTGATGGTG ATACATGCTTCTTTTTTTGTTTG
107	EX1_IFNFH32_5	Forward	AAGCAGGCTTCGCCACC AACATGACCTCACCAAATAAAC
108	EX1_IFNFH32_3	Reverse	GTGATGGT GATGGTG GTATGCCAGTTGATTTTTCAGC
109	EX1_IFNFH36_5	Forward	AAGCAGGCTTCGCCACC AACATGACCTCACCAAACAAAC
110	EX1_IFNFH36_3	Reverse	GTGATGGTGATGGTG TTCTGCTTGCTCAATTCTGC
111	EX1_IFNFH37_5	Forward	AAGCAGGCTTCGCCACC AACATGACCTCACTAAATGAAC
112	EX1_IFNFH37_3	Reverse	GTGATGGTGATGGTG ATTCTTTTTTTCTGCTCCATAAATTC
113	EX1_IFNFH39_5	Forward	AAGCAGGCTTCGCCACC TCAATGGCCAGACACCTACAAAC
114	EX1_IFNFH39_3	Reverse	GTGATGGTGATGGTG TTCTTCTACTTGATTAATTCTAC
115	EX1_IFNFH42_5	Forward	AAGCAGGCTTCGCCACCTCAATGCCAAGACACCAAAGAAC
116	EX1_IFNFH42_3	Reverse	GTGATGGTGATGGTG ATTCTTCTTTTCTACTCGATCC

TABLE V

SEQ ID NO:	NAME	DIRECTION	5'-3' SEQUENCE
117	EX2_IFNFH01_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACC AACATG ACCTCACCAAATAAAC
118	EX2_IFNFH01_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTG ATGG TGATGGTGTTTTTTTTTATTCCTTTTCTTTTGTC
119	EX2_IFNFH03_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACC AACATG ACATCACCAAATGAG
120	EX2_IFNFH03_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGCAGGTGCCTGCCACTGCAC
121	EX2_IFNFH04_5	Forward	GGGGAC AAGTTTGTACAAAAAAGCAGGCTTCGCCACC AACATG ACCTCACCAAATGAAC
122	EX2_IFNFH04_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGAGAGACTGATGCATTCTTTAG
123	EX2_IFNFH08_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACC AACATG ACCTCACCAAATGAAC
124	EX2_IFNFH08_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGATTCCGATTAATTCTACTATG
125	EX2_IFNFH10_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACC AACATG ACCTCACCAAATGAG
126	EX2_IFNFH10_3	Reverse	GGGGACCACTTTGTACAAGAAAGCTGGGTTTCAATGGTGATG GTGATGGTG TTGTTTT TTGTTGTTTTTGGTC
127	EX2_IFNFH11_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACC CACATG ACCTCAGGAAATGAAG
128	EX2_IFNFH11_3	Reverse	GGGGACCACTTTGTACAAGAAAGCTGGGTTTCAATGGTGATG GTGATGGTG TTGTTTTTTATTCTTTTTCTTTTG
129	EX2_IFNFH12_5	Forward	GGGGACAAGTTTGTACAAAAAAG CAGGCTTCGCCACC AACATG ACCTCACCAAATGAAC
130	EX2_IFNFH12_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGATCAGTTCTGCTATTAAAAAACTC
131	EX2_IFNFH13_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACC AACATG ACCTCACCAAATGAAC
132	EX2_IFNFH13_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGGGTGTGCTTCATTCTTTTATATTTTTT
133	EX2_IFNFH14_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACC AACATG ACATCAACAAAGGAAC
134	EX2_IFNFH14_3	Reverse	GGGGACCACTTTGTACAAGAAAGCTGGGTTTCAATGGTGATG GTGATGGTG TATTCTTTTTTCTC TTCTGACTG
135	EX2_IFNFH15_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACC AATATG ACCTCACCAAATGAAC
136	EX2_IFNFH15_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGTTTAAGGCCAATAACTTTTAG
137	EX2_IFNFH20_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCG CCACCAACATG CCCTTACCAAATGAGC
138	EX2_IFNFH20_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGTGATGCATTCTTCATTATAC
139	EX2_IFNFH23_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACCAACATG ACCTCACCAAATGAAC
140	EX2_IFNFH23_3	Reverse	GGGGACCACTTTGTA CAAGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGTATACTTTCAAATAGCCTGTC
141	EX2_IFNFH27_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACCAACATG ACCTCGCCTAATGAAC
142	EX2_IFNFH27_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGGTTTGCTTCCTCTGACTG
143	EX2_IFNFH31_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACCAATATG ACCTCACCAAATGAAC
144	EX2_IFNFH31_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGATACATGCTTCTTTTTTTGTTTG

TABLE V (cont.)

SEQ ID NO:	NAME	DIRECTION	5'-3' SEQUENCE
145	EX2_IFNFH32_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACCAACATG ACCTCACCAAATAAAC
146	EX2_IFNFH32_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGGTATGCCAGTTGATTTTTCAGC
147	EX2_IFNFH36_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACC AACATG ACCTCACCAAACAAAC
148	EX2_IFNFH36_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGTTCTGCTTGCTCAATTCTGC
149	EX2_IFNFH37_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACC AACATG ACCTCACTAAATGAAC
150	EX2_IFNFH37_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGATTCTTTTTTTCTGCTCCATAAATTC
151	EX2_IFNFH39_5	Forward	GGGGACAAGTTTGTACAAAAAAGCAGGCTTCGCCACC TCAATG GCCAGACACCTACAAAC
152	EX2_IFNFH39_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGTTCTTCTACTTGATTAATTCTAC
153	EX2_IFNFH42_5	Forward	GGGGAC AAGTTTGTACAAAAAAGCAGGCTTCGCCACCTCAAT GCCAAGACACCAAAGAAC
154	EX2_IFNFH42_3	Reverse	GGGGACCACTTTGTACA AGAAAGCTGGGTTTCAATGGTGATGG TGATGGTGATTCTTCTTTTCTACTCGATCC

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CLAIMS

1. An isolated polypeptide at least one activity of human IFNgamma selected from the group consisting of:

   a) amino acid sequences SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40;

   b) variants of the amino acid sequences SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40, which are at least 80% identical to said sequences;

   c) mature forms, active fragments, precursors, salts, or derivatives of the amino acid sequences given in a) or b).

2. The polypeptide of claim 1 that is a naturally occurring allelic variant of the sequences SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40.

3. The polypeptide of claim 2, wherein the variant is the translation of a single nucleotide polymorphism.

4. A fusion protein comprising a polypeptide according to any of the claims from 1 to 3.

5 The fusion proteins of claim 4 wherein said proteins further comprise one or more amino acid sequence belonging to these protein sequences: membrane-bound protein, immunoglobulin constant region, multimerization domains, extracellular proteins, signal peptide-containing proteins, export signal-containing proteins.

6 A ligand binding specifically to a polypeptide according to claim 1.

7 The ligand of claim 6 that antagonizes or inhibits the IFNgamma-related activity of a polypeptide according to any one of claims 1 to 3.

8 A ligand according to claim 7 which is a monoclonal antibody, a polyclonal antibody, a humanized antibody, an antigen binding fragment, or the extracellular domain of a membrane-bound protein.

9 The polypeptides of any of the claims from 1 to 8, wherein said polypeptides are in the form of active conjugates or complexes with a molecule chosen amongst radioactive labels, fluorescent labels, biotin, or cytotoxic agents.

10 A peptide mimetic designed on the sequence and/or the structure of a polypeptide according to any one of claims 1 to 3.

11 An isolated nucleic acid encoding for an isolated polypeptide selected from the group consisting of:

a) the polypeptides having at least one of the activity of human IFNgamma of any of the claims from 1 to 3;

b) the fusion proteins of claim 4 or 5.

12. The nucleic acid of Claim 11, comprising a DNA sequence selected from the group consisting of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35 , 37, and 39, or the complement of said DNA sequences.

13. A purified nucleic acid which:

a) hybridizes under high stringency conditions; or

b) exhibits at least about 85% identity over a stretch of at least about 30 nucleotides

with a nucleic acid selected from the group consisting of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, and 39, or a complement of said DNA sequences

14. A vector comprising a nucleic acid of any of Claims from 11 to 13.

15. The vector of claim 14, wherein said nucleic acid molecule is operatively linked to expression control sequences allowing expression in prokaryotic or eukaryotic host cells of the encoded polypeptide.

16. A process for producing cells capable of expressing a polypeptide of any the claims from 1 to 3, comprising genetically engineering cells with a vector or a nucleic acid according to any of the claims from 11 to 15.

17. A host cell transformed with a vector or a nucleic acid according to any of the claims from 11 to 15.

18. A transgenic animal cell that has been transformed with a vector or a nucleic acid according to any of the claims from 11 to 15, having enhanced or reduced expression levels of a polypeptide according to any one of claims from 1 to 3.

19. A transgenic non-human organism that has been transformed to have enhanced or reduced expression levels of a polypeptide according to any one of claims from 1 to 3.

20. A method for making a polypeptide of any the claims from 1 to 3 comprising culturing a cell of claim 17 or 18 under conditions in which the nucleic acid or vector is expressed, and recovering the polypeptide encoded by said nucleic acid or vector from cell culture.

21. A compound that enhances the expression level of a polypeptide according to any one of claims from 1 to 3 into a cell or in an animal.

22. A compound that reduces the expression level of a polypeptide according to any one of claims from 1 to 3 into a cell or in an animal.

23. The compound of claim 22 that is an antisense oligonucleotide or a small interfering RNA.

24. Purified preparations containing a polypeptide of any of the claims from 1 to 5 or claim 9, a ligand of any of the claims from 6 to 8, a peptide mimetic of claim

10, a nucleic acid of any of the claims from 11 to 15, a cell of claim 17 or 18, or a compound of any of the claims from 21 to 23.

25. Use of a polypeptide of any of the claims from 1 to 5 or claim 9, a peptide mimetic of claim 10, a nucleic acid of any of the claims from 11 to 15, a cell of claim 17 or 18, or a compound of claim 21, in the therapy or in the prevention of a disease when the increase in a human IFNgamma-related activity of a polypeptide of any of the claims from 1 to 3 is needed.

26. Pharmaceutical compositions for the treatment or prevention of diseases needing an increase in a human IFNgamma-related activity of polypeptide of any of the claims from 1 to 5 or claim 9, a peptide mimetic of claim 10, a nucleic acid of any of the claims from 11 to 15, a cell of claim 17 or 18, or a compound of claim 21, as active ingredient.

27. Process for the preparation of pharmaceutical compositions, which comprises combining polypeptide of any of the claims from 1 to 5 or claim 9, a peptide mimetic of claim 10, a nucleic acid of any of the claims from 11 to 15, a cell of claim 17 or 18, or a compound of claim 21, together with a pharmaceutically acceptable carrier.

28. Method for the treatment or prevention of diseases needing an increase in a human IFNgamma-related activity of a polypeptide of any of the claims from 1 to 3, comprising the administration of a therapeutically effective amount of polypeptide of any of the claims from 1 to 5 or claim 9, a peptide mimetic of

claim 10, a nucleic acid of any of the claims from 11 to 15, a cell of claim 17 or 18, or a compound of claim 21.

29. Use of a ligand of any of the claims from 6 to 8, or of a compound of claim 22 or 23, in the therapy or in the prevention of a disease associated to the excessive human IFNgamma-related activity of a polypeptide of any of the claims from 1 to 3.

30. Pharmaceutical compositions for the treatment or prevention of a disease associated to the excessive human IFNgamma-related activity of a polypeptide of any of the claims from 1 to 3, containing a ligand of any of the claims from 6 to 8, or of a compound of claim 22 or 23, as active ingredient.

31. Process for the preparation of pharmaceutical compositions for the treatment or prevention of diseases associated to the excessive human IFNgamma-related activity of a polypeptide of any of the claims from 1 to 3, which comprises combining a ligand of any of the claims from 6 to 8, or of a compound of claim 22 or 23, together with a pharmaceutically acceptable carrier.

32. A method for the treatment or prevention of diseases related to the polypeptide of any of the claims from 1 to 3, comprising the administration of a therapeutically effective amount of a ligand of any of the claims from 6 to 8, or of a compound of claim 22 or 23.

33. A method for screening candidate compounds effective to treat a disease related to the polypeptides of any of the claims from 1 to 3, comprising:

(a) contacting a cell of claim 17 or 18, or a transgenic non-human organism according to claim 19, having enhanced or reduced expression levels of the polypeptide, with a candidate compound; and

(b) determining the effect of the compound on the animal or on the cell.

34. A method for identifying a candidate compound as an antagonist/inhibitor or agonist/activator of a polypeptide of any of the claims 1 to 3 comprising:

(a) contacting said polypeptide, said compound, and a mammalian cell or a mammallian cell membrane capable of binding the polypeptide; and

(b) measuring whether the molecule blocks or enhances the interaction of the polypeptide, or the response that results from such interaction, with the mammalian cell or the mammalian cell membrane.

35. A method for determining the activity and/or the presence of the polypeptide of any the claims from 1 to 34 in a sample, the method comprising:

(a) providing a protein-containing sample;

(b) contacting said sample with a ligand of any of the claims from 6 to 8; and

(c) determining the presence of said ligand bound to said polypeptide.

36. A method for determining the presence or the amount of a transcript or of a nucleic acid encoding the polypeptide of any the claims from 1 to 3 in a sample, the method comprising:

(a) providing a nucleic acids-containing sample;

(b) contacting said sample with a nucleic acid of any of the claims 11 to 15; and

(c) determining the hybridization of said nucleic acid with a nucleic acid into the sample.

37. Use of the primer sequences containing any of the sequences SEQ ID NO: 41 -78 for determining the presence or the amount of a transcript or of a nucleic acid encoding a polypeptide of any the claims from 1 to 4 in a sample by Polymerase Chain Reaction.

38. A kit for measuring the activity and/or the presence of the polypeptides of any of the claims from 1 to 3 in a sample comprising one or more of the following reagents: a polypeptide of any of the claims from 1 to 5 or claim 9, a ligand of any of the claims from 6 to 8, a peptide mimetic of claim 10, a nucleic acid of any of the claims from 11 to 15, a cell of claim 17 or 18, a compound of any of the claims from 21 to 23, or a primer sequences containing any of the sequences SEQ ID NO: 41-78.

ABSTRACT

The present invention discloses novel open reading frames (ORFs) in human genome encoding for ORFs characterized for polypeptides having at least one activity of human Interferon gamma, and reagents related thereto including variants and fragments of said polypeptides, as well as the encoding nucleic acids and the ligands directed against them. The invention provides methods for identifying and making these molecules, for preparing pharmaceutical compositions containing them, and for using them in the diagnosis, prevention and treatment of diseases.

Figure 1

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                 ------------------------------------------>
IFNFH01     1    AAC ATG ACC TCA CCA AAT AAA CTA AAT AAG   30
pIFNFH01    1        Met Thr Ser Phe Asn Lys Leu Asn Lys    9

IFNFH01    31    CTA CCA GGG ACC AAC CCT GGA GAA ACA GAA   60
pIFNFH01   10    Leu Pro Gly Thr Asn Pro Gly Glu Thr Glu   19

IFNFH01    61    ATA TGT GAC CTT TTA GAT AGA GAA TTC AAA   90
pIFNFH01   20    Ile Cys Asp Leu Leu Asp Arg Glu Phe Lys   29

IFNFH01    91    ATA GCT GTG TTG AGG AAA CTC AAA AAA TAT  120
pIFNFH01   30    Ile Ala Val Leu Arg Lys Leu Lys Lys Tyr   39

IFNFH01   121    CAA GAT GAT ACA GAG AAG AAG TTC AGA ATT  150
pIFNFH01   40    Gln Asp Asp Thr Glu Lys Lys Phe Arg Ile   49

IFNFH01   151    CTA TCA GAT AAA TTT AAC AAA GAG ATT GAA  180
pIFNFH01   50    Leu Ser Asp Lys Phe Asn Lys Glu Ile Glu   59

IFNFH01   181    ATA TTA AAA AAT AAT CAA GCA GAA ATT CTG  210
pIFNFH01   60    Ile Leu Lys Asn Asn Gln Ala Glu Ile Leu   69

IFNFH01   211    GAG CTG AAA AAT TTG ACT GGA ATA CTG AAG  240
pIFNFH01   70    Glu Leu Lys Asn Leu Thr Gly Ile Leu Lys   79

IFNFH01   241    AAT GTG CCA GGG TCT TTT AAT AGC AGA ATT  270
pIFNFH01   80    Asn Val Pro Gly Ser Phe Asn Ser Arg Ile   89

IFNFH01   271    GAT GGA GCA AAA GGA AGA ATT AGT AAG CCT  300
pIFNFH01   90    Asp Gly Ala Lys Gly Arg Ile Ser Lys Pro   99

IFNFH01   301    GAA GAC AGG TTA TTT GAA AAT ACA CAG AGG  330
pIFNFH01  100    Glu Asp Arg Leu Phe Glu Asn Thr Gln Arg  109

                 <------------------------------------------
IFNFH01   331    AGA CAA AAG AAA AGG AAT AAA AAA AAA TGA  360
pIFNFH01  110    Arg Gln Lys Lys Arg Asn Lys Lys Lys stop 118
```

Figure 2

```
                 ------------------------------------------>
IFNFH03     1    AAC ATG ACA TCA CCA AAT GAG TTA AAT GAG    30
pIFNFH03    1        Met Thr Ser Pro Asn Glu Leu Asn Glu     9

IFNFH03    31    GCA GCA GGA ACT ACT CCC AAA GAA ACA GAG    60
pIFNFH03   10    Ala Ala Gly Thr Thr Pro Lys Glu Thr Glu    19

IFNFH03    61    ATA TGT GAC ATT TCA GAC AGA GAA TTC AAA    90
pIFNFH03   20    Ile Cys Asp Ile Ser Asp Arg Glu Phe Lys    29

IFNFH03    91    ATA GCT TTG TTG AAG AAA CTC AAA GAA ATT   120
pIFNFH03   30    Ile Ala Leu Leu Lys Lys Leu Lys Glu Ile    39

IFNFH03   121    CAA GAT AAT ACG GAG AAG GAA CTC AGA ATT   150
pIFNFH03   40    Gln Asp Asn Thr Glu Lys Glu Leu Arg Ile    49

IFNFH03   151    CTA TCA GAT AAA TTT AAC AAG GAG ATT GAA   180
pIFNFH03   50    Leu Ser Asp Lys Phe Asn Lys Glu Ile Glu    59

IFNFH03   181    ATG ATT AAA AAG AAC CAA GCA GAA ATT CTG   210
pIFNFH03   60    Met Ile Lys Lys Asn Gln Ala Glu Ile Leu    69

IFNFH03   211    GAG CTA AAA AAT GCA GGT GGC ATA TTG AAA   240
pIFNFH03   70    Glu Leu Lys Asn Ala Gly Gly Ile Leu Lys    79

IFNFH03   241    ATG CAT CAG AGT TGG CTG GGC ATG GTG GCT   270
pIFNFH03   80    Met His Gln Ser Trp Leu Gly Met Val Ala    89

IFNFH03   271    CAC GCC TGT AAT CCC AGT ACT TTG GGA AGC   300
pIFNFH03   90    His Ala Cys Asn Pro Ser Thr Leu Gly Ser    99

IFNFH03   301    CGA GGT GGG TGG ATC ACG AGT TCA GGA GTT   330
pIFNFH03  100    Arg Gly Gly Trp Ile Thr Ser Ser Gly Val   109

IFNFH03   331    CAA GAC CAG CCT GGC CAA GGC AGT GAA ACC   360
pIFNFH03  110    Gln Asp Gln Pro Gly Gln Gly Ser Glu Thr   119

IFNFH03   361    TCA TCT CTA CTA AAA ATA CAA AAA TTA GCT   390
pIFNFH03  120    Ser Ser Leu Leu Lys Ile Gln Lys Leu Ala   129

                 <------------------------------------------
IFNFH03   391    GGG TGC AGT GGC AGG CAC CTG TAA           414
pIFNFH03  130    Gly Cys Ser Gly Arg His Leu stop           136
```

Figure 3

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                 ------------------------------------>
IFNFH04     1    AAC ATG ACC TCA CCA AAT GAA CTA AAT AAG   30
pIFNFH04    1        Met Thr Ser Pro Asn Glu Leu Asn Lys    9

IFNFH04    31    GCA CCA GGG ACC AAT CCT GGA GAA ACA GAG   60
pIFNFH04   10    Ala Pro Gly Thr Asn Pro Gly Glu Thr Glu   19

IFNFH04    61    ATG TAT GAC CTT TCA GAC AGA GAA TTC AAA   90
pIFNFH04   20    Met Tyr Asp Leu Ser Asp Arg Glu Phe Lys   29

IFNFH04    91    ACA GCT ATT TTG AGG AAA CTC AAA GAA ATT  120
pIFNFH04   30    Thr Ala Ile Leu Arg Lys Leu Lys Glu Ile   39

IFNFH04   121    CAA GAT AAC ACA AAG AAG GAA TTC AGA ATT  150
pIFNFH04   40    Gln Asp Asn Thr Lys Lys Glu Phe Arg Ile   49

IFNFH04   151    CTA TCA GAT AAA TTT AAC AAA CAG ATC GAA  180
pIFNFH04   50    Leu Ser Asp Lys Phe Asn Lys Gln Ile Glu    59

IFNFH04   181    ATA ATT AAA AAG AAT CAA GCA GAA ATT CTA  210
pIFNFH04   60    Ile Ile Lys Lys Asn Gln Ala Glu Ile Leu    69

                                              <------
IFNFH04   211    GAG CTG AAA AAT GTA ATT GAT ATA CTA AAG  240
pIFNFH04   70    Glu Leu Lys Asn Val Ile Asp Ile Leu Lys    79

                 <------------------------------------
IFNFH04   241    AAT GCA TCA GTC TCT TGA                  258
pIFNFH04   80    Asn Ala Ser Val Ser stop                  84
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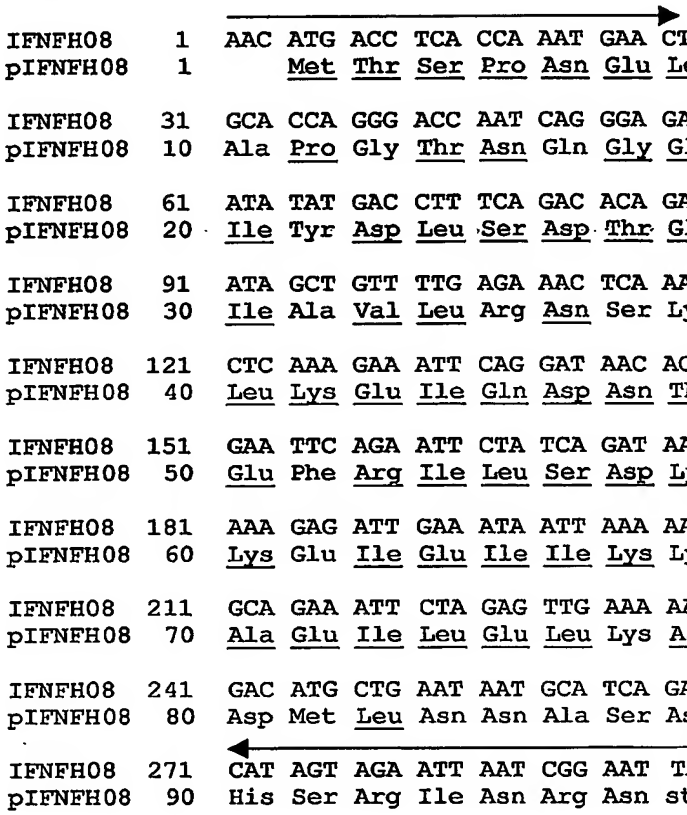
Figure 4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pIFNFH08 10 Ala Pro Gly Thr Asn Gln Gly Glu Thr Glu 19
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IFNFH08 121 CTC AAA GAA ATT CAG GAT AAC ACA GAG AAG 150
pIFNFH08 40 Leu Lys Glu Ile Gln Asp Asn Thr Glu Lys 49
IFNFH08 151 GAA TTC AGA ATT CTA TCA GAT AAA TTT AAC 180
pIFNFH08 50 Glu Phe Arg Ile Leu Ser Asp Lys Phe Asn 59
IFNFH08 181 AAA GAG ATT GAA ATA ATT AAA AAG AAT CAA 210
pIFNFH08 60 Lys Glu Ile Glu Ile Ile Lys Lys Asn Gln 69
IFNFH08 211 GCA GAA ATT CTA GAG TTG AAA AAT GCA ATT 240
pIFNFH08 70 Ala Glu Ile Leu Glu Leu Lys Asn Ala Ile 79
IFNFH08 241 GAC ATG CTG AAT AAT GCA TCA GAT TAT CTT 270
pIFNFH08 80 Asp Met Leu Asn Asn Ala Ser Asp Tyr Leu 89
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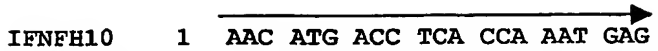
pIFNFH08 90 His Ser Arg Ile Asn Arg Asn stop 96

Figure 5



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IFNFH10     1   AAC ATG ACC TCA CCA AAT GAG GTA AAT AAG   30
pIFNFH10    1       Met Thr Ser Pro Asn Glu Val Asn Lys    9

IFNFH10    31   GTA CCA ATG ACC AAC CCT GGA GAA ACG GAG   60
pIFNFH10   10   Val Pro Met Thr Asn Pro Gly Glu Thr Glu   19

IFNFH10    61   ATA TGT GAC CTT TCA GAC CAA AAA TTA AAA   90
pIFNFH10   20   Ile Cys Asp Leu Ser Asp Gln Lys Leu Lys   29

IFNFH10    91   ATA GCT GTG ATG AGG AAA CTC AAA GAA ATT  120
pIFNFH10   30   Ile Ala Val Met Arg Lys Leu Lys Glu Ile   39

IFNFH10   121   CAA GAT AAC ACA GAG AAA GAA TTC AAA ATT  150
pIFNFH10   40   Gln Asp Asn Thr Glu Lys Glu Phe Lys Ile   49

IFNFH10   151   CTA TCA CGT AAA TTT AAC AAA AAG ATT GGA  180
pIFNFH10   50   Leu Ser Arg Lys Phe Asn Lys Lys Ile Gly   59

IFNFH10   181   TTA ATT GAA AAT AAT CAA GCA GAA ATT TTG  210
pIFNFH10   60   Leu Ile Glu Asn Asn Gln Ala Glu Ile Leu   69

IFNFH10   211   GAG CTG AAA AAT GCA ATT GGC ATA CTG AAG  240
pIFNFH10   70   Glu Leu Lys Asn Ala Ile Gly Ile Leu Lys   79

IFNFH10   241   AAT GCA TCA GAG TCC TTT AAT AGC AAT ATG  270
pIFNFH10   80   Asn Ala Ser Glu Ser Phe Asn Ser Asn Met   89

IFNFH10   271   TAT CAA GCA GAA GAC AGA ATT AGT GAG CTT  300
pIFNFH10   90   Tyr Gln Ala Glu Asp Arg Ile Ser Gl u Leu   99

IFNFH10   301   AAA TAC AGG CTA TTT GAA AAT ACA CAG TCA  330
pIFNFH10  100   Lys Tyr Arg Leu Phe Glu Asn Thr Gln Ser  109
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IFNFH10   331   GAG GAG ACC AAA AAC AAC AAA AAA CAA TGA  360
pIFNFH10  110   Glu Glu Thr Lys Asn Asn Lys Lys Gln stop 118
```

Figure 6

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                 ------------------------------------------>
IFNFH11      1   CAC ATG ACC TCA GGA AAT GAA GTA AAT AAG   30
pIFNFH11     1       Met Thr Ser Gly Asn Glu Val Asn Lys    9

IFNFH11     31   GCA CCA GGG ACC AAT CTT GGA GAA ACA GAG   60
pIFNFH11    10   Ala Pro Gly Thr Asn Leu Gly Glu Thr Glu   19

IFNFH11     61   ATA TGT GAC CTT TCA GAT ACA GAA CTC AGA   90
pIFNFH11    20   Ile Cys Asp Leu Ser Asp Thr Glu Leu Arg   29

IFNFH11     91   ATA ACT GTG TTG AGG AAA CTC AAT GAA ATT  120
pIFNFH11    30   Ile Thr Val Leu Arg Lys Leu Asn Glu Ile   39

IFNFH11    121   AAA GAT AAC ACA GAG ATG GAA TTC AGA ATT  150
pIFNFH11    40   Lys Asp Asn Thr Glu Met Glu Phe Arg Ile   49

IFNFH11    151   TTG TCA GAT AAA TTT AAG AAA GAG ATT GAA  180
pIFNFH11    50   Leu Ser Asp Lys Phe Lys Lys Glu Ile Glu   59

IFNFH11    181   ATA ATT AAA AGG AAT CAA GCA GAA ATT CTG  210
pIFNFH11    60   Ile Ile Lys Arg Asn Gln Ala Glu Ile Leu   69

IFNFH11    211   GAG CTG AAA AAT GCA ATT GGC ATA CTG AAG  240
pIFNFH11    70   Glu Leu Lys Asn Ala Ile Gly Ile Leu Lys   79

IFNFH11    241   AAT GCA TCA GAG TTT TTA AAT AGA AGA ACA  270
pIFNFH11    80   Asn Ala Ser Glu Phe Leu Asn Arg Arg Thr   89

IFNFH11    271   GAT CAA GCA GCA GAA AAA TCT AGT GAG CCT  300
pIFNFH11    90   Asp Gln Ala Ala Glu Lys Ser Ser Glu Pro   99

IFNFH11    301   GAA GAC AGA CTA TTT GAA AAT ACA CAG AGG  330
pIFNFH11   100   Glu Asp Arg Leu Phe Glu Asn Thr Gln Arg   109

                 <------------------------------------------
IFNFH11    331   TCT CAA AAG AAA AAG AAT AAA AAA CAA TAA  360
pIFNFH11   110   Ser Gln Lys Lys Lys Asn Lys Lys Gln stop  118
```

Figure 7

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                 ------------------------------------------>
IFNFH12      1   AAC ATG ACC TCA CCA AAT GAA CTG AAT AAG   30
pIFNFH12     1       Met Thr Ser Pro Asn Glu Leu Asn Lys    9

IFNFH12     31   CCA CCA GGG ACC AAT CCT GGA GAA ACA GAA   60
pIFNFH12    10   Pro Pro Gly Thr Asn Pro Gly Glu Thr Glu   19

IFNFH12     61   ATA TGT GAC CTT TCA GAC AAA GAA TTC AAA   90
pIFNFH12    20   Ile Cys Asp Leu Ser Asp Lys Glu Phe Lys   29

IFNFH12     91   ATA GCT GTG TTG AAG AAA CTC AAC GAA GCT  120
pIFNFH12    30   Ile Ala Val Leu Lys Lys Leu Asn Glu Ala   39

IFNFH12    121   CAA GAT AGC ACA GAG AAG GAA TTC AGA ATT  150
pIFNFH12    40   Gln Asp Ser Thr Glu Lys Glu Phe Arg Ile   49

IFNFH12    151   CTA TCA GAT AAA TGT AAC AAA GAC ATT AAA  180
pIFNFH12    50   Leu Ser Asp Lys Cys Asn Lys Asp Ile Lys   59

IFNFH12    181   ATA ATT AAA AAG AAT CAA GCA GAA TTT CTG  210
pIFNFH12    60   Ile Ile Lys Lys Asn Gln Ala Glu Phe Leu   69

IFNFH12    211   AAG CTG AAA GAT GCA ATT GGA ATA CTG AAG  240
pIFNFH12    70   Lys Leu Lys Asp Ala Ile Gly Ile Leu Lys   79

                 <------------------------------------------
IFNFH12    241   GAT GCA TCA GAG TTT TTT AAT AGC AGA ACT  270
pIFNFH12    80   Asp Ala Ser Glu Phe Phe Asn Ser Arg Thr   89

             <---
IFNFH12    271   GAT TGA                                 276
pIFNFH12    90   Asp stop                                 90
```
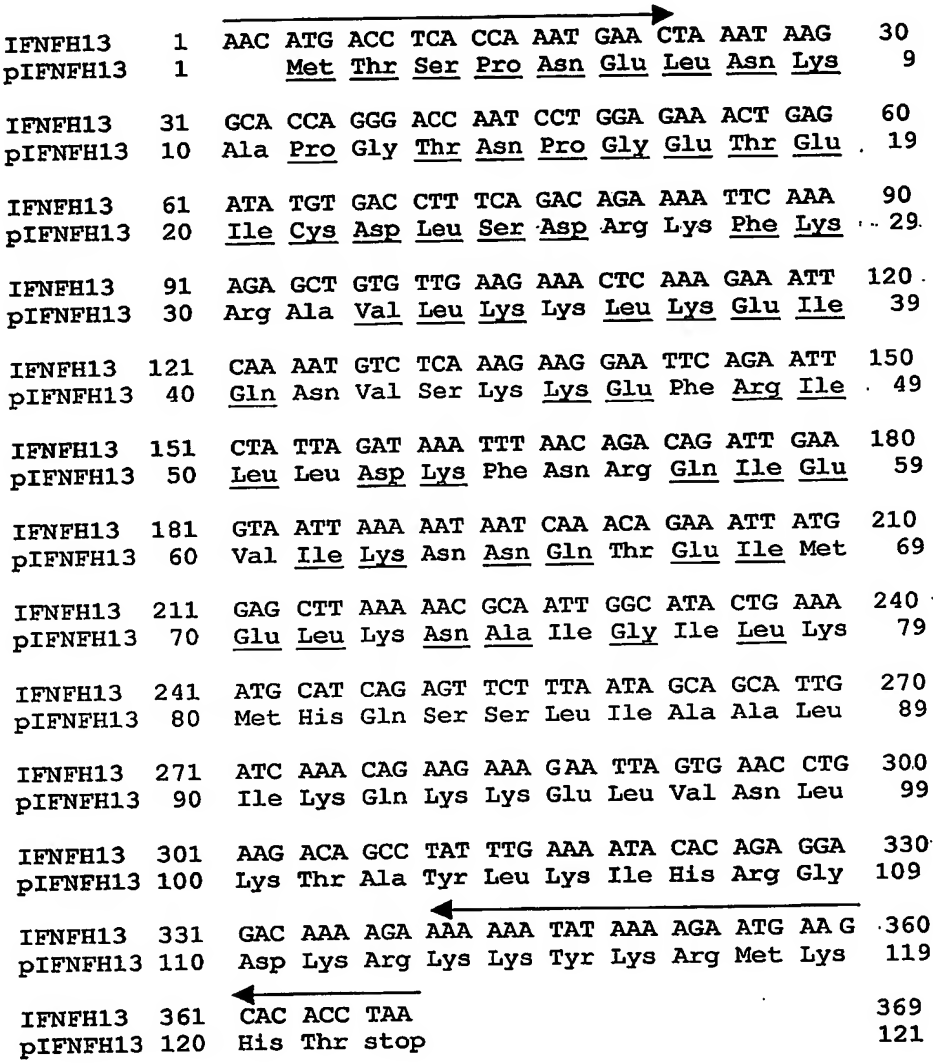

Figure 8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pIFNFH13 1 Met Thr Ser Pro Asn Glu Leu Asn Lys 9
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pIFNFH13 10 Ala Pro Gly Thr Asn Pro Gly Glu Thr Glu 19
IFNFH13 61 ATA TGT GAC CTT TCA GAC AGA AAA TTC AAA 90
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pIFNFH13 30 Arg Ala Val Leu Lys Lys Leu Lys Glu Ile 39
IFNFH13 121 CAA AAT GTC TCA AAG AAG GAA TTC AGA ATT 150
pIFNFH13 40 Gln Asn Val Ser Lys Lys Glu Phe Arg Ile 49
IFNFH13 151 CTA TTA GAT AAA TTT AAC AGA CAG ATT GAA 180
pIFNFH13 50 Leu Leu Asp Lys Phe Asn Arg Gln Ile Glu 59
IFNFH13 181 GTA ATT AAA AAT AAT CAA ACA GAA ATT ATG 210
pIFNFH13 60 Val Ile Lys Asn Asn Gln Thr Glu Ile Met 69
IFNFH13 211 GAG CTT AAA AAC GCA ATT GGC ATA CTG AAA 240
pIFNFH13 70 Glu Leu Lys Asn Ala Ile Gly Ile Leu Lys 79
IFNFH13 241 ATG CAT CAG AGT TCT TTA ATA GCA GCA TTG 270
pIFNFH13 80 Met His Gln Ser Ser Leu Ile Ala Ala Leu 89
IFNFH13 271 ATC AAA CAG AAG AAA GAA TTA GTG AAC CTG 300
pIFNFH13 90 Ile Lys Gln Lys Lys Glu Leu Val Asn Leu 99
IFNFH13 301 AAG ACA GCC TAT TTG AAA ATA CAC AGA GGA 330
pIFNFH13 100 Lys Thr Ala Tyr Leu Lys Ile His Arg Gly 109
IFNFH13 331 GAC AAA AGA AAA AAA TAT AAA AGA ATG AA G 360
pIFNFH13 110 Asp Lys Arg Lys Lys Tyr Lys Arg Met Lys 119
IFNFH13 361 CAC ACC TAA 369
pIFNFH13 120 His Thr stop 121

Figure 9

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                 ------------------------------------------>
IFNFH14     1    AAC ATG ACA TCA ACA AAG GAA CTA AAT AAG    30
pIFNFH14    1        Met Thr Ser Thr Lys Glu Leu Asn Lys     9

IFNFH14    31    GCA CCA GTA AAC AAT CCT GGA GAA ACA GAA    60
pIFNFH14   10    Ala Pro Val Asn Asn Pro Gly Glu Thr Glu    19

IFNFH14    61    CTA TGT GAC CTT TTA GAC AAA AAA TTC AAA    90
pIFNFH14   20    Leu Cys Asp Leu Leu Asp Lys Lys Phe Lys    29

IFNFH14    91    ATA GCA GTG TTG AGG AAA CTA AAA GGA ATT   120
pIFNFH14   30    Ile Ala Val Leu Arg Lys Leu Lys Gly Ile    39

IFNFH14   121    CAA AAT AAC ACA GAG AAG GAA TTC AGA ATT   150
pIFNFH14   40    Gln Asn Asn Thr Glu Lys Glu Phe Arg Ile    49

IFNFH14   151    CTA TCA GAT AAA TTT AAC AAA GAG ATT GAA   180
PIFNFH14   50    Leu Ser Asp Lys Phe Asn Lys Glu Ile Glu    59

IFNFH14   181    ATA ATT AAA AAG AAT CAA GCA GAA ACT CTG   210
pIFNFH14   60    Ile Ile Lys Lys Asn Gln Ala Glu Thr Leu    69

IFNFH14   211    GAG CTA AAA AAT GCA GTT GGC ACA CTA ACA   240
pIFNFH14   70    Glu Leu Lys Asn Ala Val Gly Thr Leu Thr    79

IFNFH14   241    AAA GCA TCA CAG TCC TTT AAA AGC AGA ATG   270
pIFNFH14   80    Lys Ala Ser Gln Ser Phe Lys Ser Arg Met    89

IFNFH14   271    GAT ATA GCA GAA AGA AGA ATT AGT GAA CTT   300
pIFNFH14   90    Asp Ile Ala Glu Arg Arg Ile Ser Glu Leu    99
                                                    <----
IFNFH14   301    AAA GAC AGG CTA TTT GAA AAT ACA GTC AGA   330
pIFNFH14  100    Lys Asp Arg Leu Phe Glu Asn Thr Val Arg   109
          <------------------------------
IFNFH14   331    AGA GAA AAA AGA ATA TAA                  348
pIFNFH14  110    Arg Glu Lys Arg Ile stop                 114
```

Figure 10

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                 ------------------------------------------>
IFNFH15     1    AAT ATG ACC TCA CCA AAT GAA CTA AAT AAG   30
pIFNFH15    1        Met Thr Ser Pro Asn Glu Leu Asn Lys    9

IFNFH15    31    GCA CCA GGG ATC AAT CCT GGG GAA ACA GAA   60
pIFNFH15   10    Ala Pro Gly Ile Asn Pro Gly Glu Thr Glu   19

IFNFH15    61    ATA TGT GAC CTT TCA GAC AGA GAA TTC ACA   90
pIFNFH15   20    Ile Cys Asp Leu Ser Asp Arg Glu Phe Thr   29

IFNFH15    91    ATA GCT GTT TCG AGG AAG CTA AAC AAA ATC  120
pIFNFH15   30    Ile Ala Val Ser Arg Lys Leu Asn Lys Ile   39

IFNFH15   121    CAA GAT AAC ATG GAG AAG GAA TTC AGA ATC  150
pIFNFH15   40    Gln Asp Asn Met Glu Lys Glu Phe Arg Ile   49

IFNFH15   151    CTA TCA GAT AAA TTT AAT GAA GAG ATT GAA  180
pIFNFH15   50    Leu Ser Asp Lys Phe Asn Glu Glu Ile Glu   59

IFNFH15   181    ATA ATT AAA AAG AAT CAA GCA GAA ATT CTG  210
pIFNFH15   60    Ile Ile Lys Lys Asn Gln Ala Glu Ile Leu   69

IFNFH15   211    GAG CTG AAA AAC GCA ATT GAC ATG TTG AAG  2 40
pIFNFH15   70    Glu Leu Lys Asn Ala Ile Asp Met Leu Lys   79

IFNFH15   241    AAT GCA TCA GAG AAT CTC ACC AGC AGA ACT  270
pIFNFH15   80    Asn Ala Ser Glu Asn Leu Thr Ser Arg Thr   89

IFNFH15   271    GAT CAA GCA AGA GAA ATA ATT AGT AAG CTT  300
pIFNFH15   90    Asp Gln Ala Arg Glu Ile Ile Ser Lys Leu   99

IFNFH15   301    GAA GAC AGG CTA TTT GAA AAC ACA AAG TCA  330
pIFNFH15  100    Glu Asp Arg Leu Phe Glu Asn Thr Lys Ser  109

IFNFH15   331    GAG GAG ACA AAT GGA AAA AGA ATA AAA TGC  360
pIFNFH15  110    Glu Glu Thr Asn Gly Lys Arg Ile Lys Cys  119

IFNFH15   361    AAT GAA GCA CAC CTA CAA GAA CTA GAA AAT  390
pIFNFH15  120    Asn Glu Ala His Leu Gln Glu Leu Glu Asn  129
                                  <------------------
IFNFH15   391    AGC TTC AAA ATG GGA AAT CTA AAA GTT ATT  420
pIFNFH15  130    Ser Phe Lys Met Gly Asn Leu Lys Val Ile  139
                 <------------
IFNFH15   421    GGC CTT AAA TAG                         432
pIFNFH15  140    Gly Leu Lys stop                        142
```
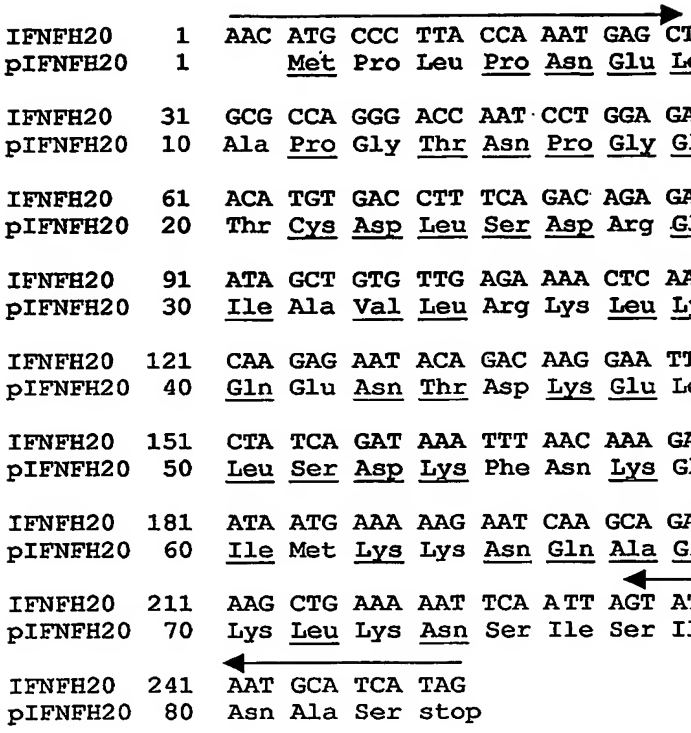

Figure 11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pIFNFH20 10 Ala Pro Gly Thr Asn Pro Gly Glu Thr Glu 19
IFNFH20 61 ACA TGT GAC CTT TCA GAC AGA GAA TTC AAA 90
pIFNFH20 20 Thr Cys Asp Leu Ser Asp Arg Glu Phe Lys 29
IFNFH20 91 ATA GCT GTG TTG AGA AAA CTC AAA GAA ATT 120
pIFNFH20 30 Ile Ala Val Leu Arg Lys Leu Lys Glu Ile 39
IFNFH20 121 CAA GAG AAT ACA GAC AAG GAA TTG AGA ATT 150
pIFNFH20 40 Gln Glu Asn Thr Asp Lys Glu Leu Arg Ile 49
IFNFH20 151 CTA TCA GAT AAA TTT AAC AAA GAA ATC AAA 180
pIFNFH20 50 Leu Ser Asp Lys Phe Asn Lys Glu Ile Lys 59
IFNFH20 181 ATA ATG AAA AAG AAT CAA GCA GAA ATT CTG 210
pIFNFH20 60 Ile Met Lys Lys Asn Gln Ala Glu Ile Leu 69
IFNFH20 211 AAG CTG AAA AAT TCA ATT AGT ATA ATG AAG 240
pIFNFH20 70 Lys Leu Lys Asn Ser Ile Ser Ile Met Lys 79
IFNFH20 241 AAT GCA TCA TAG 252
pIFNFH20 80 Asn Ala Ser stop 82

Figure 12

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                 ------------------------------------------>
IFNFH23     1    AAC ATG ACC TCA CCA AAT GAA CTG AAT AAG    30
pIFNFH23    1        Met Thr Ser Pro Asn Glu Leu Asn Lys     9

IFNFH23    31    GCA CCA GGG ACG AAT TTA GGA GAA ACA GAG    60
pIFNFH23   10    Ala Pro Gly Thr Asn Leu Gly Glu Thr Glu    19

IFNFH23    61    ATT TGT GAC CTT TCA GAC AGA GAA TTC AAG    90
pIFNFH23   20    Ile Cys Asp Leu Ser Asp Arg Glu Phe Lys    29

IFNFH23    91    AAA GCT GTG TTG CAG AAG CTC AAA GAA ATT   120
PIFNFH23   30    Lys Ala Val Leu Gln Lys Leu Lys Glu Ile    39

IFNFH23   121    CAA GAT AAC ACA GAG AAG GAG TTC AGA ATT   150
pIFNFH23   40    Gln Asp Asn Thr Glu Lys Glu Phe Arg Ile    49

IFNFH23   151    CTA TTA CAT AAA TTT AAC AAA GAG ATT AAA   180
pIFNFH23   50    Leu Leu His Lys Phe Asn Lys Glu Ile Lys    59

IFNFH23   181    ATA ATT AAA AAG AAT CAA GCA GAA ATT CTA   210
pIFNFH23   60    Ile Ile Lys Lys Asn Gln Ala Glu Ile Leu    69

IFNFH23   211    GAA GCA AAA AAT GCA ACT GAC ATA CTG ATG   240
pIFNFH23   70    Glu Ala Lys Asn Ala Thr Asp Ile Leu Met    79

IFNFH23   241    AAT GCA TCA GAC CCT ATT AAT AGC ACA ATT   270
pIFNFH     80    Asn Ala Ser Asp Pro Ile Asn Ser Thr Ile    89

IFNFH23   271    GAT GAA GCA GAA GAA AGA ATT AGT GAG CTT   300
pIFNFH     90    Asp Glu Ala Glu Glu Arg Ile Ser Glu Leu    99

                 <------------------------------------------
IFNFH23   301    GAA GAC AGG CTA TTT GAA AGT ATA TAG       327
pIFNFH23  100    Glu Asp Arg Leu Phe Glu Ser Ile stop      107
```

Figure 13

```
IFNFH25     1  AAC ATG GCC TCA CCA AAC AAA CTA AAT AAG   30
pIFNFH25    1      Met Ala Ser Pro Asn Lys Leu Asn Lys    9

IFNFH25    31  GCA CCA GAA ACC AAT CCC AAA GAG ACA GAG   60
pIFNFH25   10  Ala Pro Glu Thr Asn Pro Lys Glu Thr Glu   19

IFNFH25    61  GTA TGT GAC CTT TCA GAC AGA GAA CTC AAA   90
pIFNFH25   20  Val Cys Asp Leu Ser Asp Arg Glu Leu Lys   29

IFNFH25    91  ATA CCT GTT TTG AGG AAG TTC AAT GAA ATT  120
pIFNFH25   30  Ile Pro Val Leu Arg Lys Phe Asn Glu Ile   39

IFNFH25   121  CAA GAT AAC ACA GAG AAG GAA TTC AGA ATT  150
pIFNFH25   40  Gln Asp Asn Thr Glu Lys Glu Phe Arg Ile   49

IFNFH25   151  CTA TCA GAT AAA TTT AAC AAA GAG ATT GAA  180
pIFNFH25   50  Leu Ser Asp Lys Phe Asn Lys Glu Ile Glu   59

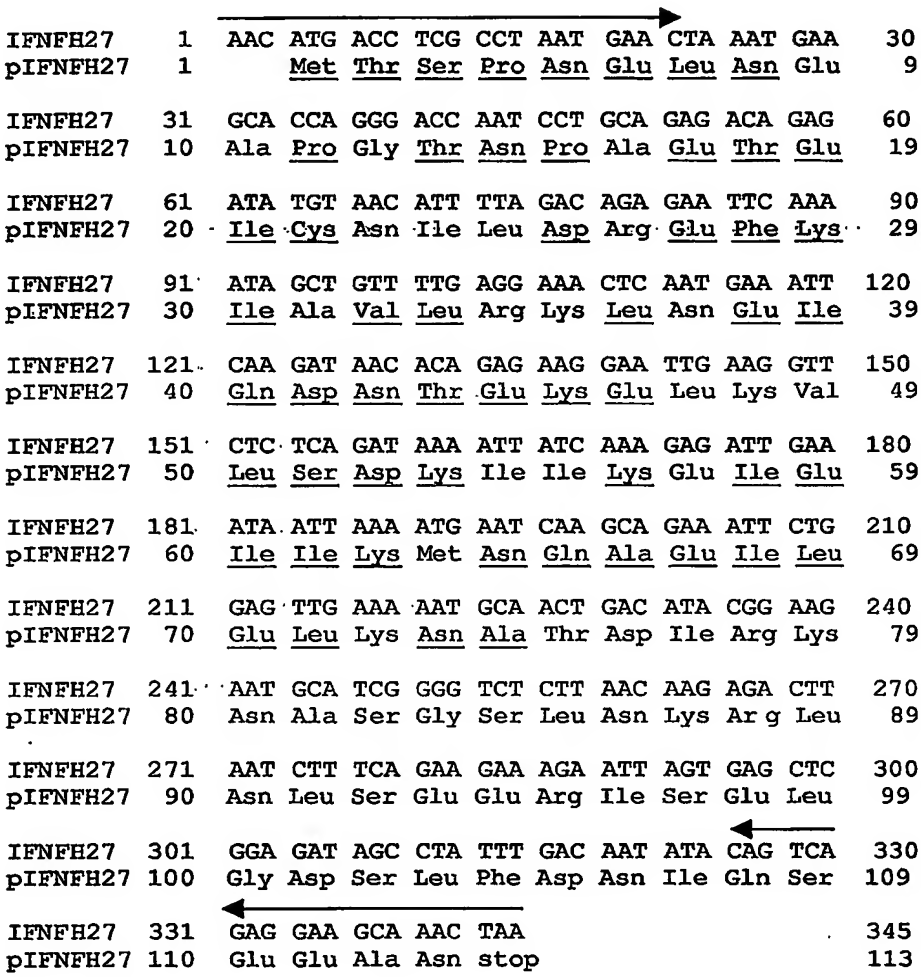
IFNFH25   181  ATA ATT AAA AAG AAT CAA GCG GAA ATT CCG  210
pIFNFH25   60  Ile Ile Lys Lys Asn Gln Ala Glu Ile Pro   69

IFNFH25   211  GAA GTG AAA AAT GCA ATT AAT ACA CTG AAG  240
pIFNFH25   70  Glu Val Lys Asn Ala Ile Asn Thr Leu Lys   79

IFNFH25   241  AAT TCA TCA GAG TCT CTT AAT AGC AGA ATT  270
pIFNFH25   80  Asn Ser Ser Glu Ser Leu Asn Ser Arg Ile   89

IFNFH25   271  GAT CAA GCA GAA TAA                     285
pIFNFH25   90  Asp Gln Ala Glu stop                    93
```

Figure 14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pIFNFH27 10 Ala Pro Gly Thr Asn Pro Ala Glu Thr Glu 19
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pIFNFH27 20 Ile Cys Asn Ile Leu Asp Arg Glu Phe Lys 29
IFNFH27 91 ATA GCT GTT TTG AGG AAA CTC AAT GAA ATT 120
pIFNFH27 30 Ile Ala Val Leu Arg Lys Leu Asn Glu Ile 39
IFNFH27 121 CAA GAT AAC ACA GAG AAG GAA TTG AAG GTT 150
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IFNFH27 151 CTC TCA GAT AAA ATT ATC AAA GAG ATT GAA 180
pIFNFH27 50 Leu Ser Asp Lys Ile Ile Lys Glu Ile Glu 59
IFNFH27 181 ATA ATT AAA ATG AAT CAA GCA GAA ATT CTG 210
pIFNFH27 60 Ile Ile Lys Met Asn Gln Ala Glu Ile Leu 69
IFNFH27 211 GAG TTG AAA AAT GCA ACT GAC ATA CGG AAG 240
pIFNFH27 70 Glu Leu Lys Asn Ala Thr Asp Ile Arg Lys 79
IFNFH27 241 AAT GCA TCG GGG TCT CTT AAC AAG AGA CTT 270
pIFNFH27 80 Asn Ala Ser Gly Ser Leu Asn Lys Arg Leu 89
IFNFH27 271 AAT CTT TCA GAA GAA AGA ATT AGT GAG CTC 300
pIFNFH27 90 Asn Leu Ser Glu Glu Arg Ile Ser Glu Leu 99
IFNFH27 301 GGA GAT AGC CTA TTT GAC AAT ATA CAG TCA 330
pIFNFH27 100 Gly Asp Ser Leu Phe Asp Asn Ile Gln Ser 109
IFNFH27 331 GAG GAA GCA AAC TAA 345
pIFNFH27 110 Glu Glu Ala Asn stop 113

Figure 15

```
                 ------------------------------------------>
IFNFH31     1    AAT ATG ACC TCA CCA AAT GAA CTA AAT AAG    30
pIFNFH31    1        Met Thr Ser Pro Asn Glu Leu Asn Lys     9

IFNFH31    31    GTA CCA GGG GCC AAT CCT GGA GAA ACA GAG    60
pIFNFH31   10    Val Pro Gly Ala Asn Pro Gly Glu Thr Glu    19

IFNFH31    61    ATT TGT GAT CAT TCA GAA AGA GAA TTC AAA    90
pIFNFH31   20    Ile Cys Asp His Ser Glu Arg Glu Phe Lys    29

IFNFH31    91    ATA ACT GTC TTG AGG AAA CTC AAA GAC ATT   120
pIFNFH31   30    Ile Thr Val Leu Arg Lys Leu Lys Asp Ile    39

IFNFH31   121    CAT GAT AAC ACA GAG AAG ACA ATC AGA ATT   150
pIFNFH31   40    His Asp Asn Thr Glu Lys Thr Ile Arg Ile    49

IFNFH31   151    CTA TCA GAT AAA TTT AAC AAA GAT ATT GAA   180
pIFNFH31   50    Leu Ser Asp Lys Phe Asn Lys Asp Ile Glu    59

IFNFH31   181    ATA ATT TTA AAA AAT CAA GAT GAT ATT CTG   210
pIFNFH31   60    Ile Ile Leu Lys Asn Gln Asp Asp Ile Leu    69

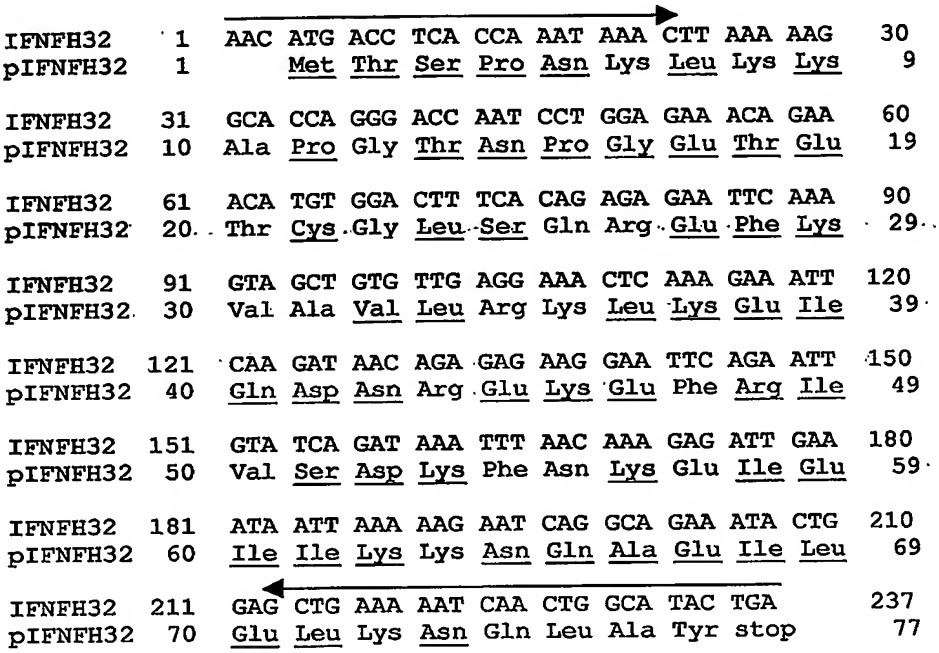
IFNFH31   211    GAG CTG GAA AAT GCA ATT GGT GTA CT G AAG   240
pIFNFH31   70    Glu Leu Glu Asn Ala Ile Gly Val Leu Lys    79

IFNFH31   241    AAT GAA TCA GGG TTC TTT AAT AGC AGG ATG   270
pIFNFH31   80    Asn Glu Ser Gly Phe Phe Asn Ser Arg Met    89

IFNFH31   271    GAT GAA GCA GAA GAA ATA ATT AGA AAG CTT   300
pIFNFH31   90    Asp Glu Ala Glu Glu Ile Ile Arg Lys Leu    99

IFNFH31   301    GAA GAC AGT TTA TTT GAA AAT ATA CAG TCA   330
pIFNFH31  100    Glu Asp Ser Leu Phe Glu Asn Ile Gln Ser   109
                                                    <----
IFNFH31   331    GAG AAG AAA GCG AAA AAA GTA AAA CAA ACA   360
pIFNFH31  110    Glu Lys Lys Ala Lys Lys Val Lys Gln Thr   119
                 <------------------------------------
IFNFH31   361    AAC AAA AAA AGA AGC ATG TAT TAG           384
pIFNFH31  120    Asn Lys Lys Arg Ser Met Tyr stop          126
```

Figure 16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pIFNFH32 10 Ala Pro Gly Thr Asn Pro Gly Glu Thr Glu 19
IFNFH32 61 ACA TGT GGA CTT TCA CAG AGA GAA TTC AAA 90
pIFNFH32 20 Thr Cys Gly Leu Ser Gln Arg Glu Phe Lys 29
IFNFH32 91 GTA GCT GTG TTG AGG AAA CTC AAA GAA ATT 120
pIFNFH32 30 Val Ala Val Leu Arg Lys Leu Lys Glu Ile 39
IFNFH32 121 CAA GAT AAC AGA GAG AAG GAA TTC AGA ATT 150
pIFNFH32 40 Gln Asp Asn Arg Glu Lys Glu Phe Arg Ile 49
IFNFH32 151 GTA TCA GAT AAA TTT AAC AAA GAG ATT GAA 180
pIFNFH32 50 Val Ser Asp Lys Phe Asn Lys Glu Ile Glu 59
IFNFH32 181 ATA ATT AAA AAG AAT CAG GCA GAA ATA CTG 210
pIFNFH32 60 Ile Ile Lys Lys Asn Gln Ala Glu Ile Leu 69
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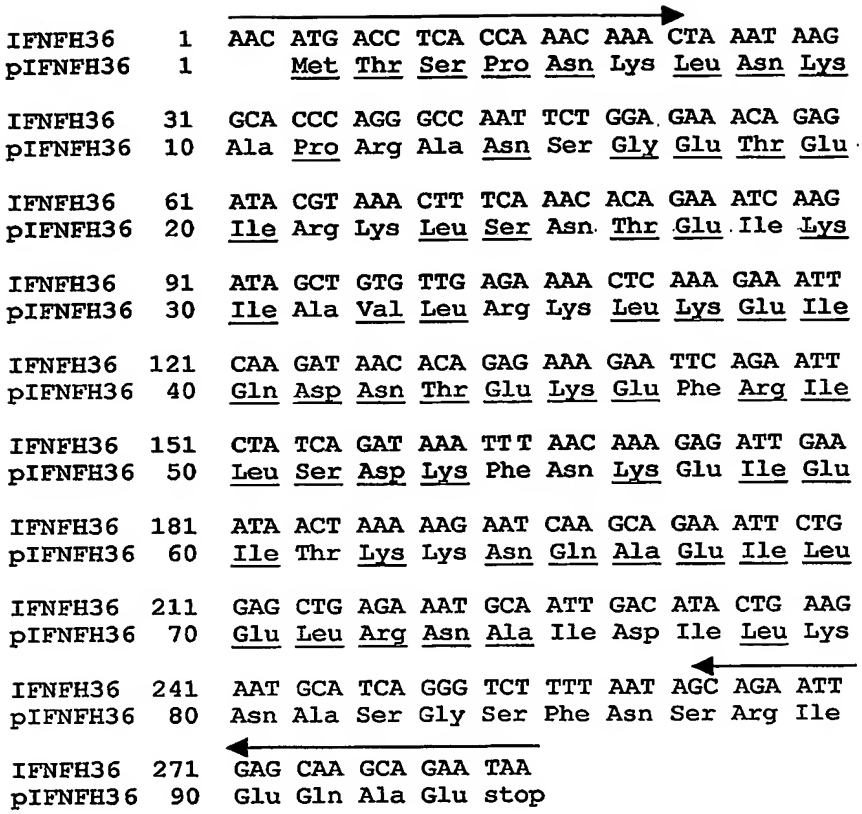
pIFNFH32 70 Glu Leu Lys Asn Gln Leu Ala Tyr stop 77

Figure 17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pIFNFH36 10 Ala Pro Arg Ala Asn Ser Gly Glu Thr Glu 19
IFNFH36 61 ATA CGT AAA CTT TCA AAC ACA GAA ATC AAG 90
pIFNFH36 20 Ile Arg Lys Leu Ser Asn Thr Glu Ile Lys 29
IFNFH36 91 ATA GCT GTG TTG AGA AAA CTC AAA GAA ATT 120
pIFNFH36 30 Ile Ala Val Leu Arg Lys Leu Lys Glu Ile 39
IFNFH36 121 CAA GAT AAC ACA GAG AAA GAA TTC AGA ATT 150
pIFNFH36 40 Gln Asp Asn Thr Glu Lys Glu Phe Arg Ile 49
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pIFNFH36 50 Leu Ser Asp Lys Phe Asn Lys Glu Ile Glu 59
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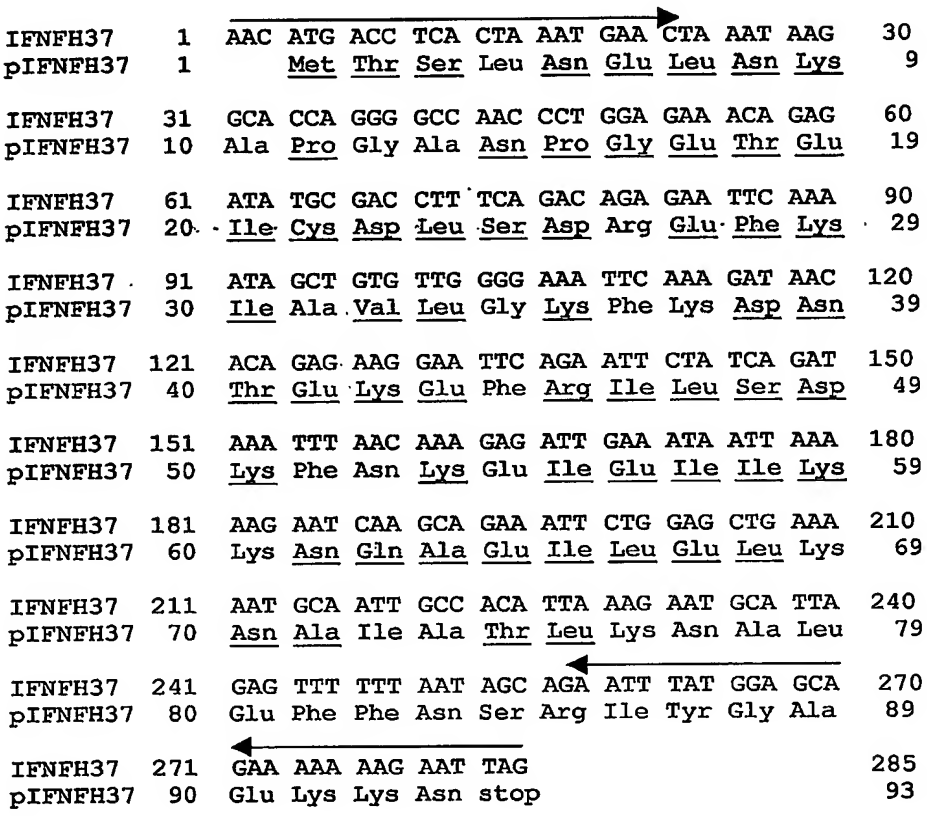
pIFNFH36 60 Ile Thr Lys Lys Asn Gln Ala Glu Ile Leu 69
IFNFH36 211 GAG CTG AGA AAT GCA ATT GAC ATA CTG AAG 240
pIFNFH36 70 Glu Leu Arg Asn Ala Ile Asp Ile Leu Lys 79
IFNFH36 241 AAT GCA TCA GGG TCT TTT AAT AGC AGA ATT 270
pIFNFH36 80 Asn Ala Ser Gly Ser Phe Asn Ser Arg Ile 89
IFNFH36 271 GAG CAA GCA GAA TAA 285
pIFNFH36 90 Glu Gln Ala Glu stop 93

Figure 18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pIFNFH37 10 Ala Pro Gly Ala Asn Pro Gly Glu Thr Glu 19
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pIFNFH37 20 Ile Cys Asp Leu Ser Asp Arg Glu Phe Lys 29
IFNFH37 91 ATA GCT GTG TTG GGG AAA TTC AAA GAT AAC 120
pIFNFH37 30 Ile Ala Val Leu Gly Lys Phe Lys Asp Asn 39
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pIFNFH37 70 Asn Ala Ile Ala Thr Leu Lys Asn Ala Leu 79
IFNFH37 241 GAG TTT TTT AAT AGC AGA ATT TAT GGA GCA 270
pIFNFH37 80 Glu Phe Phe Asn Ser Arg Ile Tyr Gly Ala 89
IFNFH37 271 GAA AAA AAG AAT TAG 285
pIFNFH37 90 Glu Lys Lys Asn stop 93

Figure 19

```
                 ------------------------------------------>
IFNFH39     1    TCA ATG GCC AGA CAC CTA CAA ACA TCC ACT    30
pIFNFH39    1        Met Ala Arg His Leu Gln Thr Ser Thr     9

IFNFH39    31    AGC ATC AAG ACC ATC CAG GAA AAT AGG ACC    60
pIFNFH39   10    Ser Ile Lys Thr Ile Gln Glu Asn Arg Thr    19

IFNFH39    61    TCA CCA AGT GAA CTA AAT AAG GCA CCA GGG    90
pIFNFH39   20    Ser Pro Ser Glu Leu Asn Lys Ala Pro Gly    29

IFNFH39    91    GCC AGT CTT GGA GAA ACA GAG ATA TGT GAT   120
pIFNFH39   30    Ala Ser Leu Gly Glu Thr Glu Ile Cys Asp    39

IFNFH39   121    CTT TCA AAC AGA GAA TTG AAA ATA GCT GTT   150
pIFNFH39   40    Leu Ser Asn Arg Glu Leu Lys Ile Ala Val    49

IFNFH39   151    TTG AGG AAA CTC AAA GAA ATT CAA GAT AGC   180
pIFNFH39   50    Leu Arg Lys Leu Lys Glu Ile Gln Asp Ser    59

IFNFH39   181    ACA GAG AAG GAA TTC AGA ATC CTA TCA GAT   210
pIFNFH39   60    Thr Glu Lys Glu Phe Arg Ile Leu Ser Asp    69

IFNFH39   211    AAA TTT AAC AAA CAA ATT GAA ATA ATT AAA   240
pIFNFH39   70    Lys Phe Asn Lys Gln Ile Glu Ile Ile Lys    79

IFNFH39   241    AAC AGT CAA GCA GAA ATT CTG GAG CTG AAA   270
pIFNFH39   80    Asn Ser Gln Ala Glu Ile Leu Glu Leu Lys    89

IFNFH39   271    AAT GCA ATT GAC TTA CTG AAG AAT GCA TCA   300
pIFNFH39   90    Asn Ala Ile Asp Leu Leu Lys Asn Ala Ser    99

                                <------------------------
IFNFH39   301    GAA TCT CCT AAT AGT AGA ATT AAT CAA GTA   330
pIFNFH39  100    Glu Ser Pro Asn Ser Arg Ile Asn Gln Val   109

          <------
IFNFH39   331    GAA GAA TGA                              339
pIFNFH39  110    Glu Glu stop                             111
```

Figure 20

```
                 ------------------------------------------>
IFNFH42     1    TCA ATG CCA AGA CAC CAA AGA ACA CCT ACT    30
pIFNFH42    1        Met Pro Arg His Gln Arg Thr Pro Thr     9

IFNFH42    31    AGA ATC AAC ACC ATC CAG GAA AAC ACG ACC    60
pIFNFH42   10    Arg Ile Asn Thr Ile Gln Glu Asn Thr Thr     19

IFNFH42    61    TCA TCA AAT GAG CTA AAT GAG GCA CCA GGG    90
pIFNFH42   20    Ser Ser Asn Glu Leu Asn Glu Ala Pro Gly     29

IFNFH42    91    ATC ACT CCT GGA GAA ACA GAG ATA TGT GAC   120
pIFNFH42   30    Ile Thr Pro Gly Glu Thr Glu Ile Cys Asp     39

IFNFH42   121    CTT TCA GAC AGA GAA TTC AAA GTA GCT GTG   150
pIFNFH42   40    Leu Ser Asp Arg Glu Phe Lys Val Ala Val     49

IFNFH42   151    TTG AGA GAG CTC AAA GAA ATT CAA GAT AAC   180
pIFNFH42   50    Leu Arg Glu Leu Lys Glu Ile Gln Asp Asn     59

IFNFH42   181    ACA GAG AAG AAA TTC AGA ATT CTA CCA GAT   210
pIFNFH42   60    Thr Glu Lys Lys Phe Arg Ile Leu Pro Asp     69

IFNFH42   211    AAA TTT ATC AAA GAG ATT GAA ATA ATT AAA   240
pIFNFH42   70    Lys Phe Ile Lys Glu Ile Glu Ile Ile Lys     79

IFNFH42   241    AAG AAT CAA TCA GAA ATT CTG GAG CTG AAA   270
pIFNFH42   80    Lys Asn Gln Ser Glu Ile Leu Glu Leu Lys     89

IFNFH42   271    AAC CCA ACT GCT GTA CTG AAG AAT GCA TCA   300
pIFNFH42   90    Asn Pro Thr Ala Val Leu Lys Asn Ala Ser     99

                                          <----------
IFNFH42   301    GAG TCC CTT AAT AGC AGA ATG GAT CGA GTA   330
pIFNFH42  100    Glu Ser Leu Asn Ser Arg Met Asp Arg Val   109

          <----------
IFNFH42   331    GAA AAG AAG AAT TAG                       345
pIFNFH42  110    Glu Lys Lys Asn stop                      113
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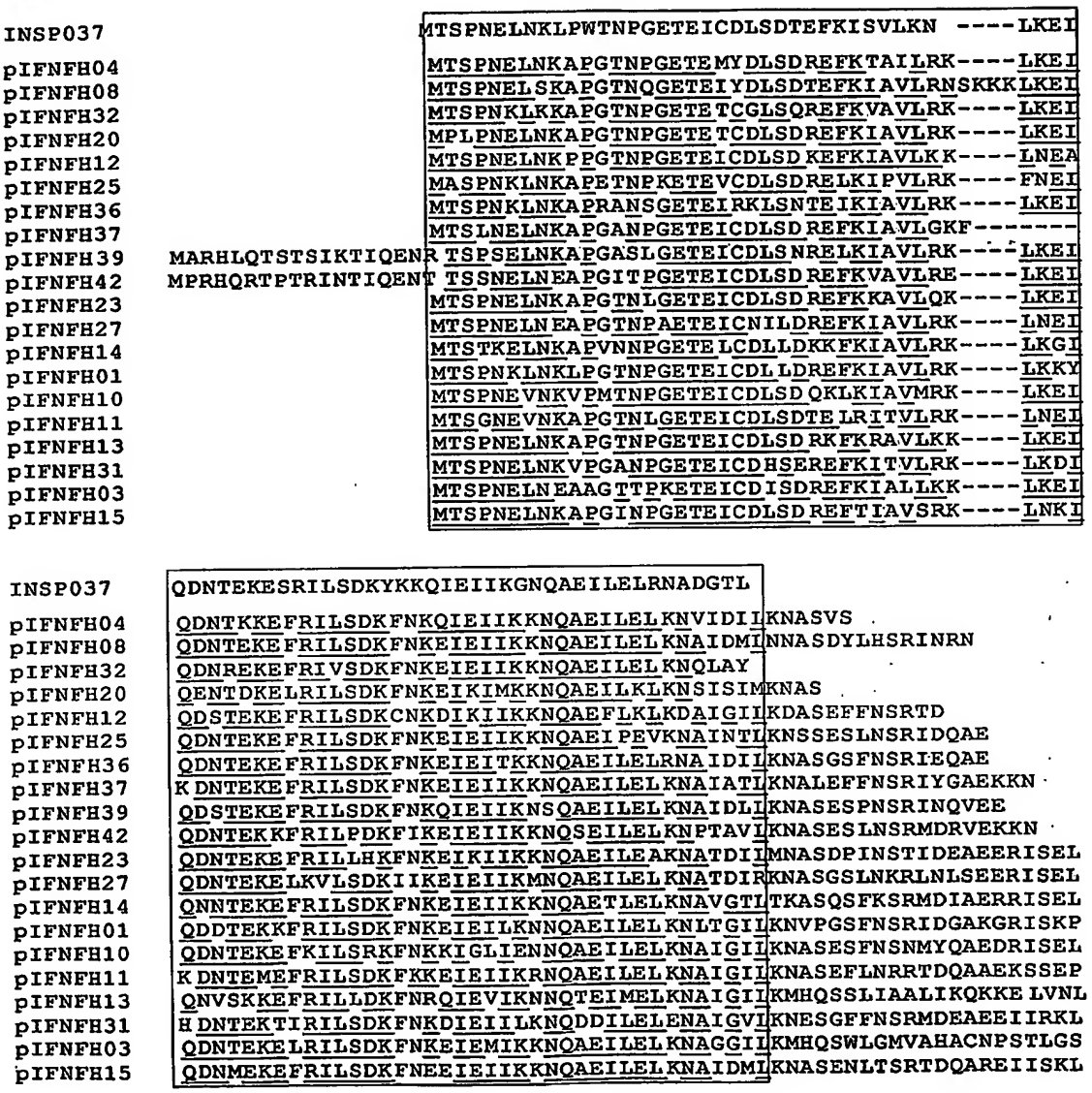
Figure 21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pIFNFH27 MTSPNELNEAPGTNPAETEICNILDREFKIAVLRK----LNEI
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pIFNFH32 QDNREKEFRIVSDKFNKEIEIIKKNQAEILELKNQLAY
pIFNFH20 QENTDKELRILSDKFNKEIKIMKKNQAEILKLKNSISIMKNAS
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pIFNFH25 QDNTEKEFRILSDKFNKEIEIIKKNQAEIPEVKNAINTLKNSSESLNSRIDQAE
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pIFNFH39 QDSTEKEFRILSDKFNKQIEIIKNSQAEILELKNAIDLLKNASESPNSRINQVEE
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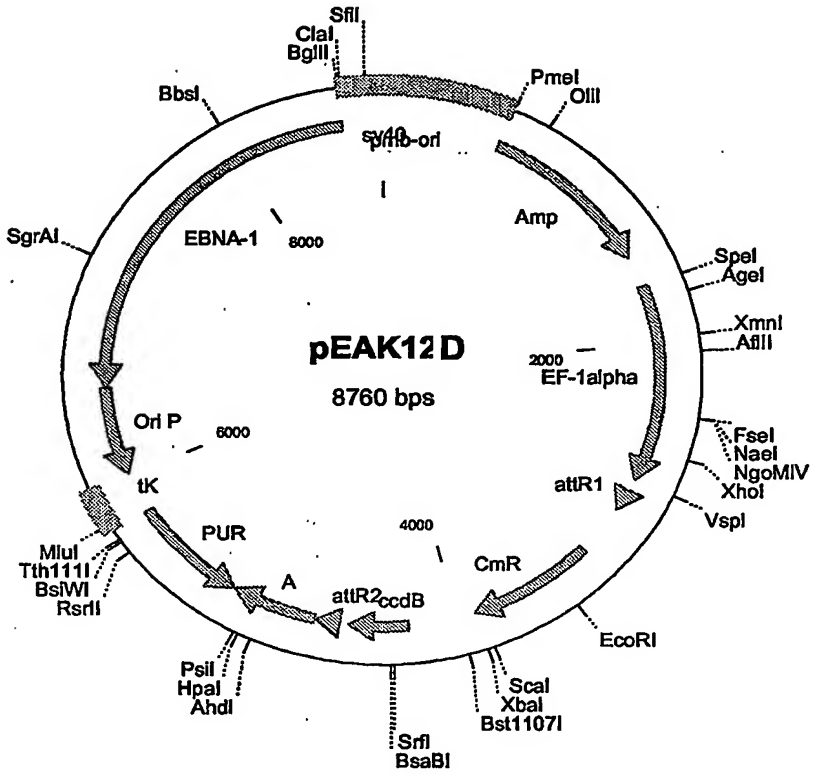
Figure 22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Leu Arg Lys Leu Lys Lys Tyr Gln Asp Asp Thr Glu Lys Lys Phe Arg
35 40 45

Ile Leu Ser Asp Lys Phe Asn Lys Glu Ile Glu Ile Leu Lys Asn Asn
50 55 60

Gln Ala Glu Ile Leu Glu Leu Lys Asn Leu Thr Gly Ile Leu Lys Asn
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Val Pro Gly Ser Phe Asn Ser Arg Ile Asp Gly Ala Lys Gly Arg Ile
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Lys Arg Asn Lys Lys Lys
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atgattaaaa agaaccaagc agaaattctg gagctaaaaa atgcaggtgg catattgaaa 240

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cgaggtgggt ggatcacgag ttcaggagtt caagaccagc ctggccaagg cagtgaaacc 360

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20 25 30

Leu Lys Lys Leu Lys Glu Ile Gln Asp Asn Thr Glu Lys Glu Leu Arg
35 40 45

Ile Leu Ser Asp Lys Phe Asn Lys Glu Ile Glu Met Ile Lys Lys Asn
50 55 60

Gln Ala Glu Ile Leu Glu Leu Lys Asn Ala Gly Gly Ile Leu Lys Met
65 70 75 80

His Gln Ser Trp Leu Gly Met Val Ala His Ala Cys Asn Pro Ser Thr
85 90 95

Leu Gly Ser Arg Gly Gly Trp Ile Thr Ser Ser Gly Val Gln Asp Gln
100 105 110

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20 25 30

Leu Arg Lys Leu Lys Glu Ile Gln Asp Asn Thr Lys Lys Glu Phe Arg
35 40 45

Ile Leu Ser Asp Lys Phe Asn Lys Gln Ile Glu Ile Ile Lys Lys Asn
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aaagagattg aaataattaa aaagaatcaa gcagaaattc tagagttgaa aaatgcaatt 240

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20 25 30

Leu Arg Asn Ser Lys Lys Lys Leu Lys Glu Ile Gln Asp Asn Thr Glu
35 40 45

Lys Glu Phe Arg Ile Leu Ser Asp Lys Phe Asn Lys Glu Ile Glu Ile
50 55 60

Ile Lys Lys Asn Gln Ala Glu Ile Leu Glu Leu Lys Asn Ala Ile Asp
65 70 75 80

Met Leu Asn Asn Ala Ser Asp Tyr Leu His Ser Arg Ile Asn Arg Asn
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20 25 30

Met Arg Lys Leu Lys Glu Ile Gln Asp Asn Thr Glu Lys Glu Phe Lys
35 40 45

Ile Leu Ser Arg Lys Phe Asn Lys Lys Ile Gly Leu Ile Glu Asn Asn
50 55 60

Gln Ala Glu Ile Leu Glu Leu Lys Asn Ala Ile Gly Ile Leu Lys Asn
65 70 75 80

Ala Ser Glu Ser Phe Asn Ser Asn Met Tyr Gln Ala Glu Asp Arg Ile
85 90 95

Ser Glu Leu Lys Tyr Arg Leu Phe Glu Asn Thr Gln Ser Glu Glu Thr
100 105 110

Lys Asn Asn Lys Lys Gln
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ataattaaaa ggaatcaagc agaaattctg gagctgaaaa atgcaattgg catactgaag 2
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aatgcatcag agtttttaaa tagaagaaca gatcaagcag cagaaaaatc tagtgagcct 3
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<213> Homo sapiens

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Glu Thr Glu Ile Cys Asp Leu Ser Asp Thr Glu Leu Arg Ile Thr Val
20 25 30

Leu Arg Lys Leu Asn Glu Ile Lys Asp Asn Thr Glu Met Glu Phe Arg
35 40 45

Ile Leu Ser Asp Lys Phe Lys Lys Glu Ile Glu Ile Ile Lys Arg Asn
50 55 60

Gln Ala Glu Ile Leu Glu Leu Lys Asn Ala Ile Gly Ile Leu Lys Asn
65 70 75 80

Ala Ser Glu Phe Leu Asn Arg Arg Thr Asp Gln Ala Ala Glu Lys Ser
85 90 95

Ser Glu Pro Glu Asp Arg Leu Phe Glu Asn Thr Gln Arg Ser Gln Lys
100 105 110

Lys Lys Asn Lys Lys Gln
115

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20

caagatagca cagagaagga attcagaatt ctatcagata aatgtaacaa agacattaaa 1
80

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76

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20 25 30

Leu Lys Lys Leu Asn Glu Ala Gln Asp Ser Thr Glu Lys Glu Phe Arg
35 40 45

Ile Leu Ser Asp Lys Cys Asn Lys Asp Ile Lys Ile Ile Lys Lys Asn
50 55 60

Gln Ala Glu Phe Leu Lys Leu Lys Asp Ala Ile Gly Ile Leu Lys Asp
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20 25 30

Leu Lys Lys Leu Lys Glu Ile Gln Asn Val Ser Lys Lys Glu Phe Arg
35 40 45

Ile Leu Leu Asp Lys Phe Asn Arg Gln Ile Glu Val Ile Lys Asn Asn
50 55 60

Gln Thr Glu Ile Met Glu Leu Lys Asn Ala Ile Gly Ile Leu Lys Met
65 70 75 80

His Gln Ser Ser Leu Ile Ala Ala Leu Ile Lys Gln Lys Lys Glu Leu
85 90 95

Val Asn Leu Lys Thr Ala Tyr Leu Lys Ile His Arg Gly Asp Lys Arg
100 105 110

Lys Lys Tyr Lys Arg Met Lys His Thr
115 120

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caaaataaca cagagaagga attcagaatt ctatcagata aatttaacaa agagattgaa 180

ataattaaaa agaatcaagc agaaactctg gagctaaaaa atgcagttgg cacactaaca 240

aaagcatcac agtcctttaa aagcagaatg gatatagcag aaagaagaat tagtgaactt 300

aaagacaggc tatttgaaaa tacagtcaga agagaaaaaa gaatataa 348

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<211> 114
<212> PRT
<213> Homo sapiens

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Glu Thr Glu Leu Cys Asp Leu Leu Asp Lys Lys Phe Lys Ile Ala Val
20 25 30

Leu Arg Lys Leu Lys Gly Ile Gln Asn Asn Thr Glu Lys Glu Phe Arg
35 40 45

Ile Leu Ser Asp Lys Phe Asn Lys Glu Ile Glu Ile Ile Lys Lys Asn
50 55 60

Gln Ala Glu Thr Leu Glu Leu Lys Asn Ala Val Gly Thr Leu Thr Lys
65 70 75 80

Ala Ser Gln Ser Phe Lys Ser Arg Met Asp Ile Ala Glu Arg Arg Ile
85 90 95

Ser Glu Leu Lys Asp Arg Leu Phe Glu Asn Thr Val Arg Arg Glu Lys
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Arg Ile

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20 25 30

Ser Arg Lys Leu Asn Lys Ile Gln Asp Asn Met Glu Lys Glu Phe Arg
35 40 45

Ile Leu Ser Asp Lys Phe Asn Glu Glu Ile Glu Ile Ile Lys Lys Asn
50 55 60

Gln Ala Glu Ile Leu Glu Leu Lys Asn Ala Ile Asp Met Leu Lys Asn
65 70 75 80

Ala Ser Glu Asn Leu Thr Ser Arg Thr Asp Gln Ala Arg Glu Ile Ile
85 90 95

Ser Lys Leu Glu Asp Arg Leu Phe Glu Asn Thr Lys Ser Glu Glu Thr
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20 25 30

Leu Arg Lys Leu Lys Glu Ile Gln Glu Asn Thr Asp Lys Glu Leu Arg
35 40 45

Ile Leu Ser Asp Lys Phe Asn Lys Glu Ile Lys Ile Met Lys Lys Asn
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Gln Ala Glu Ile Leu Lys Leu Lys Asn Ser Ile Ser Ile Met Lys Asn
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<210> 23
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20 25 30

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35 40 45

Ile Leu Leu His Lys Phe Asn Lys Glu Ile Lys Ile Ile Lys Lys Asn
50 55 60

Gln Ala Glu Ile Leu Glu Ala Lys Asn Ala Thr Asp Ile Leu Met Asn
65 70 75 80

Ala Ser Asp Pro Ile Asn Ser Thr Ile Asp Glu Ala Glu Glu Arg Ile
85 90 95

Ser Glu Leu Glu Asp Arg Leu Phe Glu Ser Ile
100 105

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<211> 285
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caagataaca cagagaagga attcagaatt ctatcagata aatttaacaa agagattgaa 1
80

ataattaaaa agaatcaagc ggaaattccg gaagtgaaaa atgcaattaa tacactgaag 2
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Glu Thr Glu Val Cys Asp Leu Ser Asp Arg Glu Leu Lys Ile Pro Val
20 25 30

Leu Arg Lys Phe Asn Glu Ile Gln Asp Asn Thr Glu Lys Glu Phe Arg
35 40 45

Ile Leu Ser Asp Lys Phe Asn Lys Glu Ile Glu Ile Ile Lys Lys Asn
50 55 60

Gln Ala Glu Ile Pro Glu Val Lys Asn Ala Ile Asn Thr Leu Lys Asn
65 70 75 80

Ser Ser Glu Ser Leu Asn Ser Arg Ile Asp Gln Ala Glu
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20

caagataaca cagagaagga attgaaggtt ctctcagata aaattatcaa agagattgaa 1
80

ataattaaaa tgaatcaagc agaaattctg gagttgaaaa atgcaactga catacggaag 2
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<211> 113
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<400> 28

Met Thr Ser Pro Asn Glu Leu Asn Glu Ala Pro Gly Thr Asn Pro Ala
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Glu Thr Glu Ile Cys Asn Ile Leu Asp Arg Glu Phe Lys Ile Ala Val
20 25 30

Leu Arg Lys Leu Asn Glu Ile Gln Asp Asn Thr Glu Lys Glu Leu Lys
35 40 45

Val Leu Ser Asp Lys Ile Ile Lys Glu Ile Glu Ile Ile Lys Met Asn
50 55 60

Gln Ala Glu Ile Leu Glu Leu Lys Asn Ala Thr Asp Ile Arg Lys Asn
65 70 75 80

Ala Ser Gly Ser Leu Asn Lys Arg Leu Asn Leu Ser Glu Glu Arg Ile
85 90 95

Ser Glu Leu Gly Asp Ser Leu Phe Asp Asn Ile Gln Ser Glu Glu Ala
100 105 110

Asn

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<212> DNA
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60

atttgtgatc attcagaaag agaattcaaa ataactgtct tgaggaaact caaagacatt 1
20

catgataaca cagagaagac aatcagaatt ctatcagata aatttaacaa agatattgaa 1
80

ataattttaa aaaatcaaga tgatattctg gagctggaaa atgcaattgg tgtactgaag 2
40

aatgaatcag ggttctttaa tagcaggatg gatgaagcag aagaaataat tagaaagctt 3
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<400> 30

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1 5 10 15

Glu Thr Glu Ile Cys Asp His Ser Glu Arg Glu Phe Lys Ile Thr Val
20 25 30

Leu Arg Lys Leu Lys Asp Ile His Asp Asn Thr Glu Lys Thr Ile Arg
35 40 45

Ile Leu Ser Asp Lys Phe Asn Lys Asp Ile Glu Ile Ile Leu Lys Asn
50 55 60

Gln Asp Asp Ile Leu Glu Leu Glu Asn Ala Ile Gly Val Leu Lys Asn
65 70 75 80

Glu Ser Gly Phe Phe Asn Ser Arg Met Asp Glu Ala Glu Glu Ile Ile
85 90 95

Arg Lys Leu Glu Asp Ser Leu Phe Glu Asn Ile Gln Ser Glu Lys Lys
100 105 110

Ala Lys Lys Val Lys Gln Thr Asn Lys Lys Arg Ser Met Tyr
115 120 125

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caagataaca gagagaagga attcagaatt gtatcagata aatttaacaa agagattgaa 180

ataattaaaa agaatcaggc agaaatactg gagctgaaaa atcaactggc atactga 237

<210> 32
<211> 77
<212> PRT
<213> Homo sapiens

<400> 32

Met Thr Ser Pro Asn Lys Leu Lys Lys Ala Pro Gly Thr Asn Pro Gly
1 5 10 15

Glu Thr Glu Thr Cys Gly Leu Ser Gln Arg Glu Phe Lys Val Ala Val
20 25 30

Leu Arg Lys Leu Lys Glu Ile Gln Asp Asn Arg Glu Lys Glu Phe Arg
35 40 45

Ile Val Ser Asp Lys Phe Asn Lys Glu Ile Glu Ile Ile Lys Lys Asn
50 55 60

Gln Ala Glu Ile Leu Glu Leu Lys Asn Gln Leu Ala Tyr

65 70 75

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caagataaca cagagaaaga attcagaatt ctatcagata aatttaacaa agagattgaa 180

ataactaaaa agaatcaagc agaaattctg gagctgagaa atgcaattga catactgaag 240

aatgcatcag ggtcttttaa tagcagaatt gagcaagcag aataa 285

<210> 34
<211> 93
<212> PRT
<213> Homo sapiens

<400> 34

Met Thr Ser Pro Asn Lys Leu Asn Lys Ala Pro Arg Ala Asn Ser Gly
1 5 10 15

Glu Thr Glu Ile Arg Lys Leu Ser Asn Thr Glu Ile Lys Ile Ala Val
20 25 30

Leu Arg Lys Leu Lys Glu Ile Gln Asp Asn Thr Glu Lys Glu Phe Arg
35 40 45

Ile Leu Ser Asp Lys Phe Asn Lys Glu Ile Glu Ile Thr Lys Lys Asn
50 55 60

Gln Ala Glu Ile Leu Glu Leu Arg Asn Ala Ile Asp Ile Leu Lys Asn
65 70 75 80

Ala Ser Gly Ser Phe Asn Ser Arg Ile Glu Gln Ala Glu
85 90

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<212> DNA
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<400> 35
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60

atatgcgacc tttcagacag agaattcaaa atagctgtgt tggggaaatt caaagataac 1
20

acagagaagg aattcagaat tctatcagat aaatttaaca aagagattga ataattaaaa 1
80

aagaatcaag cagaaattct ggagctgaaa aatgcaattg ccacattaaa gaatgcatta 2
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gagtttttta atagcagaat ttatggagca gaaaaaaaga attag 2
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<210> 36
<211> 93
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<213> Homo sapiens

<400> 36

Met Thr Ser Leu Asn Glu Leu Asn Lys Ala Pro Gly Ala Asn Pro Gly
1 5 10 15

Glu Thr Glu Ile Cys Asp Leu Ser Asp Arg Glu Phe Lys Ile Ala Val
20 25 30

Leu Gly Lys Phe Lys Asp Asn Thr Glu Lys Glu Phe Arg Ile Leu Ser
35 40 45

Asp Lys Phe Asn Lys Glu Ile Glu Ile Ile Lys Lys Asn Gln Ala Glu
50 55 60

Ile Leu Glu Leu Lys Asn Ala Ile Ala Thr Leu Lys Asn Ala Leu Glu
65 70 75 80

Phe Phe Asn Ser Arg Ile Tyr Gly Ala Glu Lys Lys Asn
85 90

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<211> 339
<212> DNA
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tcaccaagtg aactaaataa ggcaccaggg gccagtcttg gagaaacaga gatatgtgat 1
20

ctttcaaaca gagaattgaa aatagctgtt ttgaggaaac tcaaagaaat tcaagatagc 1
80

acagagaagg aattcagaat cctatcagat aaatttaaca aacaaattga aataattaaa 2
40

aacagtcaag cagaaattct ggagctgaaa aatgcaattg acttactgaa gaatgcatca 3
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gaatctccta atagtagaat taatcaagta gaagaatga 3
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<210> 38
<211> 111
<212> PRT
<213> Homo sapiens

<400> 38

Met Ala Arg His Leu Gln Thr Ser Thr Ser Ile Lys Thr Ile Gln Glu
1 5 10 15

Asn Arg Thr Ser Pro Ser Glu Leu Asn Lys Ala Pro Gly Ala Ser Leu
20 25 30

Gly Glu Thr Glu Ile Cys Asp Leu Ser Asn Arg Glu Leu Lys Ile Ala
35 40 45

Val Leu Arg Lys Leu Lys Glu Ile Gln Asp Ser Thr Glu Lys Glu Phe
50 55 60

Arg Ile Leu Ser Asp Lys Phe Asn Lys Gln Ile Glu Ile Ile Lys Asn
65 70 75 80

Ser Gln Ala Glu Ile Leu Glu Leu Lys Asn Ala Ile Asp Leu Leu Lys

85 90 95

Asn Ala Ser Glu Ser Pro Asn Ser Arg Ile Asn Gln Val Glu Glu
100 105 110

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tcatcaaatg agctaaatga ggcaccaggg atcactcctg gagaaacaga gatatgtgac 1
20

ctttcagaca gagaattcaa agtagctgtg ttgagagagc tcaaagaaat tcaagataac 1
80

acagagaaga aattcagaat tctaccagat aaatttatca aagagattga ataattaaaa 2
40

aagaatcaat cagaaattct ggagctgaaa aacccaactg ctgtactgaa gaatgcatca 3
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gagtccctta atagcagaat ggatcgagta gaaaagaaga attag 3
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<210> 40
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<212> PRT
<213> Homo sapiens

<400> 40

Met Pro Arg His Gln Arg Thr Pro Thr Arg Ile Asn Thr Ile Gln Glu
1 5 10 15

Asn Thr Thr Ser Ser Asn Glu Leu Asn Glu Ala Pro Gly Ile Thr Pro
20 25 30

Gly Glu Thr Glu Ile Cys Asp Leu Ser Asp Arg Glu Phe Lys Val Ala
35 40 45

Val Leu Arg Glu Leu Lys Glu Ile Gln Asp Asn Thr Glu Lys Lys Phe
50 55 60

Arg Ile Leu Pro Asp Lys Phe Ile Lys Glu Ile Glu Ile Ile Lys Lys
65 70 75 80

Asn Gln Ser Glu Ile Leu Glu Leu Lys Asn Pro Thr Ala Val Leu Lys
85 90 95

Asn Ala Ser Glu Ser Leu Asn Ser Arg Met Asp Arg Val Glu Lys Lys
100 105 110

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<400> 42
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21

<210> 43
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29

<210> 44
<211> 22
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<400> 44
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<210> 45
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<400> 45
aacatgacct caccaaatga ac
22

<210> 46
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<400> 46
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<400> 47
aacatgacct caccaaatga ac
22

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22

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<400> 58
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aacatgacct caccaaataa ac
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<210> 77
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<400> 87
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<400> 93
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<400> 98
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<210> 99
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<210> 101
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<400> 101
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<210> 106
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40

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<210> 115
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<400> 115
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<210> 116
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<400> 116
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37

<210> 117
<211> 59
<212> DNA
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<400> 117
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59

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<211> 77
<212> DNA
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<400> 118
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attccttttc ttttgtc
77

<210> 119
<211> 58
<212> DNA
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<400> 119
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58

<210> 120
<211> 70
<212> DNA
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60

gccactgcac

70

<210> 121
<211> 59
<212> DNA
<213> synthetic construct

<400> 121
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59

<210> 122
<211> 72
<212> DNA
<213> synthetic construct

<400> 122
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tgcattcttt ag
72

<210> 123
<211> 59
<212> DNA
<213> synthetic construct

<400> 123
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59

<210> 124
<211> 72
<212> DNA
<213> synthetic construct

<400> 124
ggggaccact ttgtacaaga aagctgggtt tcaatggtga tggtgatggt gattccgatt
60

aattctacta tg
72

<210> 125
<211> 58
<212> DNA
<213> synthetic construct

<400> 125
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58

<210> 126
<211> 73
<212> DNA
<213> synthetic construct

<400> 126
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60

gttgtttttg gtc
73

<210> 127
<211> 59
<212> DNA
<213> synthetic construct

<400> 127
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59

<210> 128
<211> 75
<212> DNA
<213> synthetic construct

<400> 128
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75

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<211> 59
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<210> 130
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<212> DNA
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<400> 130
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60

gctattaaaa aactc
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<211> 59
<212> DNA
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<400> 131
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59

<210> 132
<211> 78
<212> DNA
<213> synthetic construct

<400> 132
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60

cattctttta tatttttt
78

<210> 133
<211> 59
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59

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74

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aataactttt ag
72

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<211> 59
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<400> 137
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59

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Leu Lys Asn Leu Lys Glu Ile Gln Asp Asn Thr Glu Lys Glu Ser Arg
35 40 45

Ile Leu Ser Asp Lys Tyr Lys Lys Gln Ile Glu Ile Ile Lys Gly Asn
50 55 60

Gln Ala Glu Ile Leu Glu Leu Arg Asn Ala Asp Gly Thr Leu
65 70 75